LESSON 10
Nonlinear Processes

OBJECTIVES

After completing Lesson 10, you should be able to:

1. Describe the relationship of both drug concentration and area under the plasma drug concentration versus time curve (AUC) to the dose for a nonlinear, zero-order process.
2. Explain the various biopharmaceutic processes that can result in nonlinear pharmacokinetics.
3. Describe how hepatic enzyme saturation can result in nonlinear pharmacokinetics.
4. Use the Michaelis–Menten model for describing nonlinear pharmacokinetics.
5. Describe V_{max} and K_m.
6. Use the Michaelis–Menten model to predict plasma drug concentrations.
7. Use the $t_{90\%}$ equation to estimate the time required for 90% of the steady-state concentration to be reached.

Until now, we have used a major assumption in constructing models for drug pharmacokinetics: drug clearance remains constant with any size dose. This is the case only when drug elimination processes are first order (as described in previous lessons). With a first-order elimination process, as the dose of drug increases, the plasma concentrations observed and the AUC increase proportionally. That is, if the dose is doubled, the plasma concentration and AUC also double (**Figure 10-1**).

Because the increase in plasma concentration and AUC is linear with drug dose in first-order processes, this concept is referred to as *linear pharmacokinetics*. When these linear relationships are present, they are used to predict drug dosage. For example, if a 100-mg daily dose of a drug produces a steady-state peak plasma concentration of 10 mg/L, we know that a 200-mg daily dose will result in a steady-state plasma concentration of 20 mg/L. (Note that *linear* does not refer to the plot of natural log of plasma concentration versus time.)

With some drugs (e.g., phenytoin and aspirin), however, the relationships of drug dose to plasma concentrations and AUC are not linear. As the drug dose increases, the peak concentration and the resulting AUC do not increase proportionally (**Figure 10-2**). Therefore, such drugs are said to follow nonlinear, zero-order, or dose-dependent pharmacokinetics (i.e., the pharmacokinetics change with the dose given). Just as with drugs following linear pharmacokinetics, it is important to predict the plasma drug concentrations of drugs following zero-order pharmacokinetics. In this lesson, we discuss methods to characterize drugs that follow nonlinear pharmacokinetics.

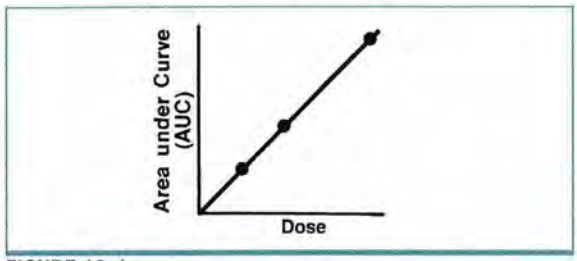

FIGURE 10-1.
Relationship of AUC to drug dose with first-order elimination, where clearance is not influenced by dose.

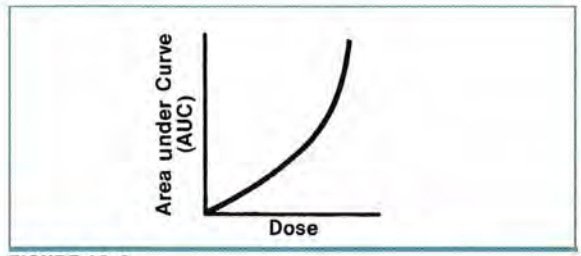

FIGURE 10-2.
Relationship of AUC to drug dose with dose-dependent pharmacokinetics.

Nonlinear pharmacokinetics may refer to several different processes, including absorption, distribution, and renal or hepatic elimination (**Table 10-1**). For example, with nonlinear absorption, the fraction of drug in the gastrointestinal (GI) tract that is absorbed per minute changes with the amount of drug present. Even though absorption and distribution can be nonlinear, the term *nonlinear pharmacokinetics* usually refers to the processes of drug elimination.

When a drug exhibits nonlinear pharmacokinetics, usually the processes responsible for drug elimination are saturable at therapeutic concentrations. These elimination processes may include renal tubular secretion (as seen with penicillins) and hepatic enzyme metabolism (as seen with phenytoin). When an elimination process is saturated, any increase in drug dose results in a disproportionate increase in the plasma concentrations achieved because the amount of drug that can be eliminated over time cannot increase. This situation is contrary to first-order linear processes, in which an increase in drug dosage results in an increase in the amount of drug eliminated over any given period.

Of course, most elimination processes are capable of being saturated if enough drug is administered. However, for most drugs, the doses administered do not cause the elimination processes to approach their limitations.

Clinical Correlate

Many drugs exhibit mixed-order pharmacokinetics, displaying first-order pharmacokinetics at low drug concentrations and zero-order pharmacokinetics at high concentrations. It is important to know the drug concentration at which a drug order switches from first to zero. Phenytoin is an example of a drug that switches order at therapeutic concentrations, whereas theophylline does not switch until concentrations reach the toxic range.

For a typical drug having dose-dependent pharmacokinetics, with saturable elimination, the plasma drug concentration versus time plot after a dose may appear as shown in **Figure 10-3**.

TABLE 10-1. Drugs Having Dose- or Time-Dependent Pharmacokinetics

Process	Agent	Mechanism
Absorption	Riboflavin, methotrexate, gabapentin	Saturable gut wall transport
	Penicillins	Saturable decomposition in GI tract
Distribution	Methotrexate	Saturable transport into and out of tissues
	Salicylates	Saturable protein binding
Renal elimination	Penicillin G	Active tubular secretion
	Ascorbic acid	Active reabsorption
Extrarenal elimination	Carbamazepine	Enzyme induction
	Theophylline, phenytoin	Saturable metabolism

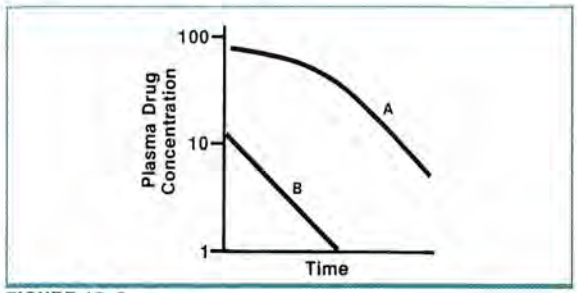

FIGURE 10-3.
Dose-dependent clearance of enzyme-saturable drugs.

After a large dose is administered, an initial slow elimination phase (clearance decreases with higher plasma concentration) is followed by a much more rapid elimination at lower concentrations (curve A). However, when a small dose is administered (curve B), the capacity of the elimination process is not reached, and the elimination rate remains constant. At high concentrations, the elimination rate approaches that of a zero-order process (i.e., the amount of drug eliminated over a given period remains constant, but the fraction eliminated changes). At low concentrations, the elimination rate approaches that of a first-order process (i.e., the amount of drug eliminated over a given time changes, but the fraction of drug eliminated remains constant).

A model that has been used extensively in biochemistry to describe the kinetics of saturable enzyme systems is known as *Michaelis–Menten kinetics* (for its developers). This system describes the relationship of an enzyme to the substrate (in this case, the drug molecule). In clinical pharmacokinetics, it allows prediction of plasma drug concentrations resulting from administration of drugs with saturable elimination (e.g., phenytoin).

The equation used to describe Michaelis–Menten pharmacokinetics is:

$$\text{drug elimination rate} = \frac{-dC}{dt} = \frac{V_{max}C}{K_m + C}$$

where $-dC/dt$ is the rate of drug concentration decline at time t and is determined by V_{max}, the theoretical maximum rate of the elimination process. K_m is the drug concentration when the rate of elimination is half the maximum rate, and C is the total plasma drug concentration.

V_{max} is expressed in units of amount per unit of time (e.g., milligrams per day) and represents the maximum amount of drug that can be eliminated in the given time period. For drugs metabolized by the liver, V_{max} can be determined by the quantity or efficiency of metabolizing enzymes. This parameter will vary, depending on the drug and individual patient.

K_m, the Michaelis constant, is expressed in units of concentration (e.g., mg/L) and is the drug concentration at which the rate of elimination is half the maximum rate (V_{max}). In simplified terms, K_m is the concentration above which saturation of drug metabolism is likely.

V_{max} and K_m are related to the plasma drug concentration and the rate of drug elimination as shown in **Figure 10-4**. When the plasma drug concentration is less than K_m, the rate of drug elimination follows first-order pharmacokinetics. In other words, the amount of drug eliminated per hour directly increases with the plasma drug concentration. When the plasma drug concentration is much less than K_m, the first-order elimination rate constant (K) for drugs with nonlinear pharmacokinetics is approximated by V_{max}; therefore, as V_{max} increases (e.g., by hepatic enzyme induction), K increases.

With drugs having saturable elimination, as plasma drug concentrations increase, drug elimination approaches its maximum rate. When the plasma concentration is much greater than K_m, the rate of drug elimination is approximated by V_{max}, and elimination proceeds at close to a zero-order process.

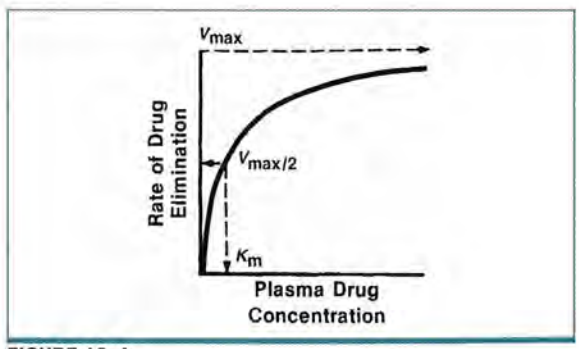

FIGURE 10-4.
Relationship of drug elimination rate to plasma drug concentration with saturable elimination.

Next, we consider how V_{max} and K_m can be calculated and how these determinations may be used to predict plasma drug concentrations in patients.

Calculation of V_{max}, K_m, and Plasma Concentration and Dose

For drugs that have saturable elimination at the plasma concentrations readily achieved with therapeutic doses (e.g., phenytoin), prediction of the plasma concentrations achieved by a given dose is important. For these predictions, it is necessary to estimate V_{max} and K_m. Therefore, we must apply the Michaelis–Menten equation presented earlier in this lesson:

$$\frac{-dC}{dt} = \frac{V_{max}C}{K_m + C}$$

The change in drug concentration over time is related to the Michaelis–Menten parameters V_{max}, K_m, and the plasma drug concentration (C). We know that at steady state (after multiple drug doses) the rate of drug loss from the body (milligrams removed per day) is equal to the amount of drug being administered (daily dose). In the Michaelis–Menten equation, $-dC/dt$ indicates the rate of drug loss from the body; therefore, at steady state:

$$\frac{-dC}{dt} = \text{daily drug dose} = \frac{V_{max}C}{K_m + C}$$

Now we have an equation that relates V_{max}, K_m, plasma drug concentration, and daily dose (at steady state). To use this relationship, it is first helpful to transform the equation to a straight-line form:

10-1 $$\text{daily dose} = \frac{V_{max}C}{K_m + C}$$

$$\text{daily dose}\,(K_m + C) = V_{max}C$$

$$\text{daily dose}\,(K_m) + \text{daily dose}\,(C) = V_{max}C$$

$$\text{daily dose}\,(C) = V_{max}C - \text{daily dose}\,(K_m)$$

Then:

$$\text{daily dose} = -K_m(\text{daily dose}/C) + V_{max}$$

$$Y\,(\text{slope}) = mX + b\,(\text{intercept})$$

So the relationship of the Michaelis–Menten parameters, C, and dose can be expressed as a straight line (**Figure 10-5**). If the straight line can be defined, then V_{max} and K_m can be determined; if V_{max} and K_m are known, then the plasma concentrations at steady state resulting from any given dose can be estimated.

To define the line, it is necessary to know the steady-state concentrations achieved at a minimum of two different doses. For example, a patient receiving 300 mg of phenytoin per day achieved a steady-state concentration (trough) of 9 mg/L; when the daily dose was increased to 400 mg/day, a steady-state concentration of 16 mg/L was achieved. The data for this patient can be plotted as shown in **Figure 10-6**. Then a line is drawn between the two points, intersecting the y-axis. The y-intercept equals V_{max} (observed to be 700 mg/day), and the slope of the line equals $-K_m$.

Calculating K_m

10-2 $$\text{slope} = -K_m = \frac{\text{dose}_{initial} - \text{dose}_{increased}}{\text{dose}/C_{initial} - \text{dose}/C_{increased}}$$

$$= \frac{300\ \text{mg/day} - 400\ \text{mg/day}}{\left(\frac{300\ \text{mg/day}}{9\ \text{mg/L}} - \frac{400\ \text{mg/day}}{16\ \text{mg/L}}\right)}$$

$$= \frac{-100\ \text{mg/day}}{33.3\ \text{L/day} - 25\ \text{L/day}}$$

$$= -12.0\ \text{mg/L}$$

So K_m equals 12 mg/L.

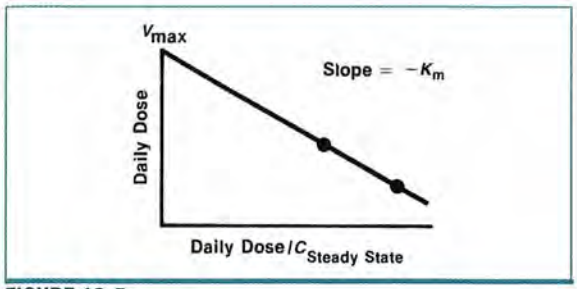

FIGURE 10-5.
Linear plot of the Michaelis–Menten equation.

Calculating Dose

Knowing V_{max} and K_m, we can then predict the dose necessary to achieve a given steady-state concentration or the concentration resulting from a given dose. If we wish to increase the steady-state plasma concentration to 20 mg/L, we can use the Michaelis–Menten equation to predict the necessary dose:

$$\text{dose} = \frac{V_{max} C}{K_m + C}$$

$$= \frac{(700 \text{ mg/day})(20 \text{ mg/L})}{12 \text{ mg/L} + 20 \text{ mg/L}}$$

$$= \frac{14{,}000 \text{ mg}^2/(\text{day} \times \text{L})}{32 \text{ mg/L}}$$

$$= 437 \text{ mg/day}$$

Note how units cancel out to yield mg/day.

Calculating Steady-State Concentration from This K_m and Dose

If we wish to predict the steady-state plasma concentration that would result if the dose is increased to 500 mg/day, we can rearrange the Michaelis–Menten equation and solve for C:

10-3 $$C = \frac{K_m(\text{daily dose})}{V_{max} - \text{daily dose}}$$

$$= \frac{12 \text{ mg/L}\ (500 \text{ mg/day})}{700 \text{ mg/day} - 500 \text{ mg/day}}$$

$$= \frac{12 \text{ mg/L}\ (500 \text{ mg/day})}{200 \text{ mg/day}}$$

$$= 30 \text{ mg/L}$$

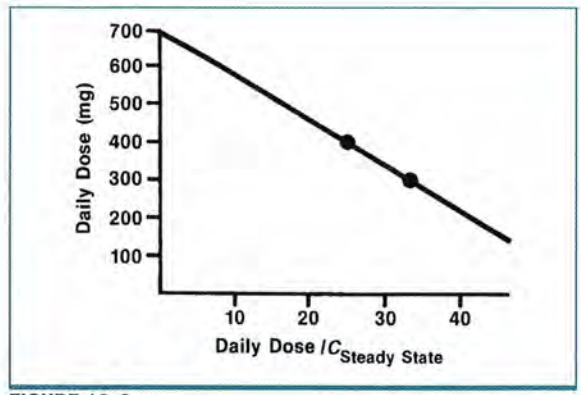

FIGURE 10-6.
Plot of patient data using two steady-state plasma phenytoin concentrations at two dose levels.

See Lesson 15 for examples of how these calculations are applied.

Clinical Correlate

When performing this calculation using sodium phenytoin or fosphenytoin, be sure to convert doses to their phenytoin free-acid equivalent before substituting these values into the equation. To convert, multiply the daily dose by 0.92 (92% free phenytoin). Fosphenytoin injection, although containing only 66% phenytoin free acid, is actually labeled in phenytoin sodium equivalents such that the 0.92 factor also applies to this product.

The preceding example demonstrates how plasma drug concentrations and drug dose can be predicted. However, it also shows that for drugs like phenytoin, with saturable elimination, when plasma concentrations are above K_m, small dose increases can result in large increases in the steady-state plasma concentration.

When clearance changes with plasma concentration, there is no true half-life as with first-order elimination. As clearance changes, the elimination rate changes as does the time to reach steady state. With high doses and high plasma concentrations (and resulting lower clearance), the time to reach steady state is much longer than with low doses and low plasma concentrations (**Figure 10-7**). Theoret-

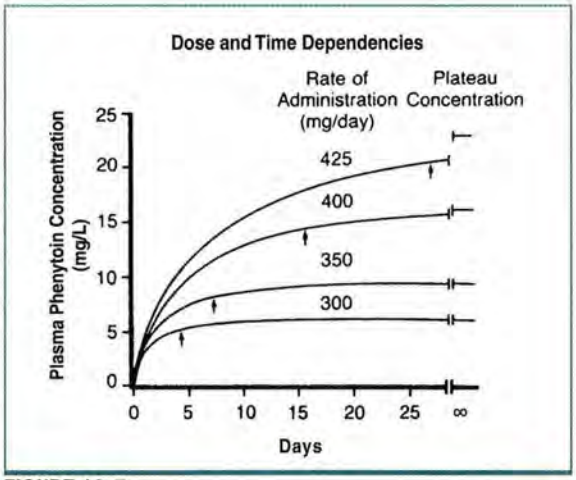

FIGURE 10-7.
Time to reach $t_{90\%}$ (represented by arrows) at different daily dosages.

ically, if the dose is greater than V_{max}, steady state will never be reached.

Because clearance and half-life are concentration-dependent factors, a traditional time to steady-state value cannot be calculated. Instead, the Michaelis–Menten equation can be rearranged to provide an equation that estimates the time required (in days) for 90% of the steady-state concentration to be reached ($t_{90\%}$), as shown below for phenytoin (where the dose equals the daily dose):

10-4 $$t_{90\%} = \frac{K_m(V)}{(V_{max} - \text{daily dose})^2}[2.3V_{max} - 0.9\ \text{dose}]$$

From the previous example, when dose = 300 mg/day, V_{max} = 700 mg/day, and K_m = 12 mg/L, volume of distribution (V) can be estimated as 0.65 L/kg body weight, or (0.65 × 77 kg body weight) = 50 L.

$$t_{90\%} = \frac{12\ \text{mg/L}\ (50\ \text{L})}{(700\ \text{mg/day} - 300\ \text{mg/day})^2}[2.3(700\ \text{mg/day}) - 0.9(300\ \text{mg/day})]$$

$$= \frac{600\ \text{mg}}{(400\ \text{mg/day})^2}[1610\ \text{mg/day} - 270\ \text{mg/day}]$$

$$= (0.00375\ \text{day}^2/\text{mg})(1340\ \text{mg/day})$$

$$= 5.0\ \text{days}$$

When the dose is increased to 400 mg/day:

$$t_{90\%} = \frac{12\ \text{mg/L}\ (50\ \text{L})}{(700\ \text{mg/day} - 300\ \text{mg/day})^2}[2.3(700\ \text{mg/day}) - 0.9(400\ \text{mg/day})]$$

$$= \frac{600\ \text{mg}}{(300\ \text{mg/day})^2}[1610\ \text{mg/day} - 360\ \text{mg/day}]$$

$$= (0.0067\ \text{day}^2/\text{mg})(1250\ \text{mg/day})$$

$$= 8.38\ \text{days}$$

We can see that as the dose is increased, it takes a longer time to reach steady state, drug continues to accumulate, and the plasma drug concentration continues to rise. When this occurs with a drug such as phenytoin, toxic effects (e.g., ataxia and nystagmus) probably will be observed if the high dosage is given on a regular basis.

Clinical Correlate

The $t_{90\%}$ equation will provide only a rough estimate of when 90% of steady state has been reached, and its accuracy is dependent on the K_m value used. Other ways to check to see if a patient is at steady state are to examine two levels drawn approximately a week apart. If these levels are ±10% of each other, then you can assume steady state. Additionally, it is safe to wait at least 2 weeks (and preferably 4 weeks) after beginning or changing a dose before obtaining new steady-state levels.

REVIEW QUESTIONS

10-1. Which drug pairs demonstrate nonlinear pharmacokinetics?

A. phenytoin and aspirin
B. penicillin G and gentamicin
C. acetaminophen and sulfonamides
D. A and B

10-2. Linear pharmacokinetics means that the plot of plasma drug concentration versus time after a dose is a straight line.

A. True
B. False

10-3. When hepatic metabolism becomes saturated, any increase in drug dose will lead to a proportionate increase in the plasma concentration achieved.

A. True
B. False

10-4. When the rate of drug elimination proceeds at half the maximum rate, the drug concentration is known as:

A. V_{max}
B. K_m
C. $\frac{1}{2}V_{max}$
D. $(V_{max})(C)$

10-5. At very high concentrations—concentrations much higher than the drug's K_m—drugs are more likely to exhibit first-order elimination.

A. True
B. False

10-6. Which of the equations below describes the form of the Michaelis–Menten equation that relates daily drug dose to V_{max}, K_m, and the steady-state plasma drug concentration?

A. daily dose = $-K_m$(daily dose/C)(V_{max})
B. daily dose = $-K_m$(daily dose/C) + V_{max}
C. daily dose = $-K_m$(daily dose × C) + V_{max}
D. daily dose = $-K_m$ – (daily dose/C) + V_{max}

The following information is for **Questions 10-7 to 10-11**. A patient, JH, is administered phenytoin free acid, 300 mg/day for 2 months (assume steady state is achieved), and a plasma concentration determined just before a dose is 10 mg/L. The phenytoin dose is then changed to 400 mg/day; 2 months after the dose change, the plasma concentration determined just before a dose is 18 mg/L. Assume that the volume of distribution of phenytoin is 45 L.

10-7. Calculate K_m for this patient.

A. 12.5 mg/L
B. 25 mg/L
C. 37.5 mg/L
D. 10 mg/L

10-8. For the same patient, JH, determine V_{max}.

A. 123 mg/day
B. 900 mg/day
C. 500 mg/day
D. 678 mg/day

10-9. For the case of JH above, plot both concentrations on a daily dose/C versus V_{max} plot and then determine this patient's V_{max}.

A. approximately 550 mg/day
B. approximately 400 mg/day
C. approximately 675 mg/day
D. approximately 800 mg/day

10-10. After the dose of 400 mg/day is begun, how long will it take to reach 90% of the steady-state plasma concentration?

A. approximately 14 days
B. approximately 9 days
C. approximately 30 days
D. approximately 90 days

10-11. If the patient, JH, misunderstood the dosage instructions and consumed 500 mg/day of phenytoin, what steady-state plasma concentration would result?

A. 29.4 mg/L

B. 36.8 mg/L

C. 27.2 mg/L

D. 19.6 mg/L

ANSWERS

10-1. A. CORRECT ANSWER

B, C, D. *Incorrect answers*

10-2. A. *Incorrect answer*

B. CORRECT ANSWER. *Linear pharmacokinetics* means that the AUC and plasma concentrations achieved are directly related to the size of the dose administered. Drugs with linear pharmacokinetics may exhibit plasma concentrations versus time plots that are not straight lines, as with multicompartment drugs.

10-3. A. *Incorrect answer*

B. CORRECT ANSWER. There will be a disproportionate increase in the plasma concentration achieved because the amount of drug that can be eliminated over time cannot increase.

10-4. A. *Incorrect answer.* V_{max} is the maximum rate of hepatic metabolism.

B. CORRECT ANSWER

C. *Incorrect answer.* $\frac{1}{2}V_{max}$ is only one-half of the maximum hepatic metabolism and does not relate K_m to V_{max}.

D. *Incorrect answer.* $(V_{max})(C)$ is only the numerator of the Michaelis–Menten equation.

10-5. A. *Incorrect answer*

B. CORRECT ANSWER. At very low concentrations, drugs are more likely to exhibit first-order kinetics because hepatic enzymes are usually not yet saturated, whereas at higher concentrations, enzymes saturate, making zero-order kinetics more likely.

10-6. A, C, D. *Incorrect answers*

B. CORRECT ANSWER

10-7. A. CORRECT ANSWER. The K_m is calculated from the slope of the line above:

$$\text{slope} = -K_m = \frac{\text{dose}_1 - \text{dose}_2}{\text{dose}_1/C_1 - \text{dose}_2/C_2}$$

$$= \frac{300\ \text{mg/day} - 400\ \text{mg/day}}{\left(\frac{300\ \text{mg/day}}{10\ \text{mg/L}} - \frac{400\ \text{mg/day}}{18\ \text{mg/L}}\right)}$$

$$= \frac{-100\ \text{mg/day}}{30\ \text{L/day} - 22\ \text{L/day}}$$

$$= \frac{-100\ \text{mg/day}}{8\ \text{L/day}}$$

$$= -12.5\ \text{mg/L}$$

So K_m equals 12.5 mg/L.

B, C, D. *Incorrect answers.* Use dose pairs of 300 and 400 and concentration pairs of 10 and 18 to calculate K_m.

10-8. A, C. *Incorrect answers.* Try again; you probably made a math error.

B. *Incorrect answer.* Try again, and use either set of dose and concentration pairs (i.e., 300 and 10 or 400 and 18).

D. CORRECT ANSWER.

$$\text{daily dose} = -K_m(\text{daily dose}/C) + V_{max}$$

$$400 = (-12.5)(400/18) + V_{max}$$

$$400 = (-12.5)(22.22) + V_{max}$$

$$400 = -277.77 + V_{max}$$

$$677.77 = V_{max}$$

10-9. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. See **Figure 10-8** for a plot of the daily dose versus daily dose/C.

10-10. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. The time to reach steady state is calculated by:

$$t_{90\%} = \frac{K_m(V)}{(V_{max} - \text{dose})^2}[2.3V_{max} - 0.9\ \text{dose}]$$

$$= \frac{12.5\ \text{mg/L}\ (45\ \text{L})}{(670\ \text{mg/day} - 400\ \text{mg/day})^2}[2.3(670\ \text{mg/day}) - 0.9(400\ \text{mg/day})]$$

$$= \frac{562.5\ \text{mg}}{(270\ \text{mg/day})^2}[1541\ \text{mg/day} - 360\ \text{mg/day}]$$

$$= (0.00772\ \text{day}^2/\text{mg})(1181\ \text{mg/day})$$

$$= 9.11\ \text{days}$$

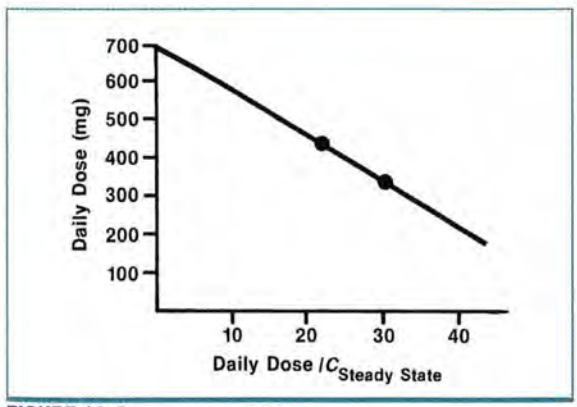

FIGURE 10-8.
Daily dose versus daily dose divided by steady-state concentration.

10-11. A. *Incorrect answer.* Perhaps you used a 400-mg dose instead of a 500-mg dose.

B. CORRECT ANSWER. The steady-state plasma concentration resulting from a daily dose of 500 mg would be estimated from the line equation as follows:

$$\text{daily dose} = -K_m(\text{dose}/C) + V_{max}$$

$$500\ \text{mg/day} = -12.5\ \text{mg/L}\left(\frac{500\ \text{mg/day}}{C}\right) + 670\ \text{mg/day}$$

Rearranging gives:

$$\frac{-170\ \text{mg/day}}{-12.5\ \text{mg/L}} = \frac{500\ \text{mg/day}}{C}$$

$$13.6\ \text{L/day} = \frac{500\ \text{mg/day}}{C}$$

$$\frac{13.6\ \text{L/day}}{500\ \text{mg/day}} = \frac{1}{C}$$

$$0.0272\ \text{L/mg} = \frac{1}{C}$$

$$C = 36.8\ \text{mg/L}$$

C, D. *Incorrect answers.* You may have made a simple math error.

Discussion Points

D-1. When using the Michaelis–Menten equation, examine what happens when daily dose is much lower than V_{max}, and when it exceeds V_{max}.

D-2. When using the $t_{90\%}$ equation, examine what happens to $t_{90\%}$ when dose greatly exceeds V_{max}.

D-3. Using two steady-state plasma drug concentrations and two doses to solve for a new K_m, V_{max}, and dose using the Michaelis–Menten equation, examine the values of K_m and V_{max} obtained using this process. Are these values close to the actual patient population parameters?

D-4. Discuss several practical methods to determine when a nonlinear drug has reached steady state.

D-5. Examine the time to 90% equation and note the value of K_m that is used in this equation. Substitute several different phenytoin K_m values based on a range of population values (i.e., from approximately 1 to 15 mg/L) and describe the effect this has on your answer. Based on this observation, what value of K_m would you use when trying to approximate the $t_{90\%}$ for a newly begun dose of phenytoin?

D-6. Discuss the patient variables that can affect the pharmacokinetic calculation of a nonlinear drug when using two plasma drug concentrations obtained from two different doses.

D-7. Examine the package insert for Cerebyx® (fosphenytoin) and answer the following questions:

A. What salt is this product?

B. What percent phenytoin sodium is it?

C. What percent phenytoin free acid is it?

D. How many milligrams of Cerebyx® is equal to 100 mg of sodium phenytoin injection?

E. What therapeutic advantage does this product offer?

LESSON 11

Pharmacokinetic Variation and Model-Independent Relationships

OBJECTIVES

After completing Lesson 11, you should be able to:

1. Identify the various sources of pharmacokinetic variation.
2. Explain how the various sources of pharmacokinetic variation affect pharmacokinetic parameters.
3. Describe how to apply pharmacokinetic variation in a clinical setting.
4. Name the potential sources of error in the collection and assay of drug samples.
5. Explain the clinical importance of correct sample collection, storage, and assay.
6. Describe ways to avoid or minimize errors in the collection and assay of drug samples.
7. Explain the basic concepts and calculations of the model-independent pharmacokinetic parameters of total body clearance, mean residence time (MRT), volume of distribution at steady state, and formation clearance.

Sources of Pharmacokinetic Variation

An important reason for pharmacokinetic drug monitoring is that a drug's effect may vary considerably among individuals given the same dose. These differences in drug effect are sometimes related to differences in pharmacokinetics. Some factors that may affect drug pharmacokinetics are discussed below. However, irrespective of pharmacokinetics, drug effects may vary among individuals because of differences in drug sensitivity.

Age

At extremes of age, major organ functions may be considerably reduced compared with those of healthy young adults. In neonates (particularly if premature) and the elderly, renal function and the capacity for renal drug excretion may be greatly reduced. Neonates and the elderly are also more likely to have reduced hepatic function. Renal function declines at a rate of approximately 1 mL/minute/year after the age of 40 years. In the neonate, renal function rapidly progresses in infancy to equal or exceed that of adults. Pediatric patients may have an increased rate of clearance because a child's drug metabolism rate is increased compared to adults. When dosing a drug for a child, the drug may need to be administered more frequently.

Other changes also occur with aging. Compared with adults, the neonate has a higher proportion of body mass made up of water and a lower proportion of body fat. The elderly are likely to have a lower proportion of body water and lean tissue (**Figure 11-1**). Both of these changes—organ function and body makeup—affect the disposition of drugs and how they are used. Reduced function of the organs of drug elimination generally requires that doses of drugs eliminated by the affected organ be given less frequently. With alterations in body water or fat content, the dose of drugs that distribute into those tissues must be altered. For drugs that distribute into body water, the neonatal dose may be larger per kilogram of body weight than in an adult.

Disease States

Drug disposition is altered in many disease states, but the most common examples involve the kidneys and liver, as they are the major organs of drug elimination. In patients with major organ dysfunction, drug clearance decreases and, subsequently, drug half-life lengthens. Some diseases, such as renal failure or cirrhosis, may even result in fluid retention and an increased volume of drug distribution.

Alterations in drug clearance and volume of distribution require adjustments in the dose administered and/or the dosing interval. For most drugs, when clearance is decreased but the volume of distribution is relatively unchanged, the dose administered may be similar to that in a healthy person although the dosing interval may need to be increased. Alternatively, smaller doses could be administered over a shorter dosing interval. When the volume of distribution is altered, the dosing interval can often remain the same but the dose administered should change in proportion to the change in volume of distribution.

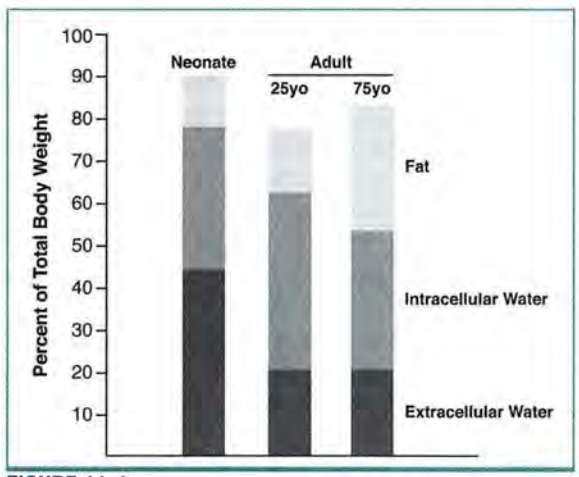

FIGURE 11-1.
Effect of age on body composition.

Clinical Correlate

When adjusting a dose of a drug that follows first-order elimination, if you do not change the dosing interval, then the new dose can be calculated using various simple ratio and proportion techniques. For example, if gentamicin peak and trough serum drug concentrations (in a patient receiving 120 mg every 12 hours) were 9 and 2.3 mcg/mL, respectively, then a new dose can be calculated: "if 120 mg gives a peak of 9, then X mg will give a desired peak of 6," yielding an answer of 80 mg every 12 hours. Likewise, one can check to see if this trough would be acceptable with this new dose: "if 120 mg gives a trough of 2.3, then 80 mg will give a trough of X," yielding an answer of 1.5 mcg/mL.

EXAMPLE

Effect of Volume of Distribution and Impaired Renal/Hepatic Function on Drug Dose

A 23-year-old male experienced a major traumatic injury from a motor vehicle accident. On the third day after injury, his renal function is determined to be good (creatinine clearance = 120 mL/minute), and his weight has increased from 63 kg on admission to 83 kg. Note that fluid accumulation (as evidenced by weight gain) is an expected result of traumatic injury. He is treated with gentamicin for gram-negative bacteremia.

An initial gentamicin dose of 100 mg is given over 1 hour, and a peak concentration of 2.5 mg/L is determined. Four hours after the peak, the plasma concentration is determined to be 0.6 mg/L, and the elimina-

tion rate constant and the volume of distribution are determined to be 0.36 hr^{-1} and 33.6 L, respectively. This volume of 33.6 L equals 0.40 L/kg compared to a typical *V* of 0.2–0.3 L/kg. In this case, the patient's gentamicin elimination rate constant is similar to that found in people with normal renal function, but the volume of distribution is much greater. To maintain a peak plasma gentamicin concentration of 6–8 mg/L, a much larger dose would have to be administered at a dosing interval of 6 or 8 hours. Using the multiple-dose infusion equation from Lesson 5 (see **Equation 5-1**), we would find that a dose as high as 220 mg given every 6 hours would be necessary to achieve the desired plasma concentrations.

On the other hand, we would expect patients with impaired renal function to have a lower creatinine clearance and, therefore, a smaller elimination rate constant compared to patients with normal renal function. A smaller than normal elimination rate constant would produce a longer half-life and would require an increase in the dosage interval.

In patients with both impaired renal function and abnormal volume of distribution values, the dose and dosing interval should be adjusted accordingly.

Just as renal dysfunction may alter the dosage requirement for drugs eliminated renally, hepatic dysfunction alters the dosage requirement for hepatically metabolized or excreted drugs. For example, the daily dose of theophylline must be reduced in patients with liver dysfunction. With this agent, however, a consistent plasma concentration (as opposed to a large difference in peak and trough plasma concentrations) is desired. Therefore, with liver dysfunction, smaller doses of theophylline than usual are generally administered but at the usual dosage intervals (two to four times daily). For a continuous intravenous infusion, the infusion rate must be reduced.

Genetic Factors, Pharmacogenetics, and Pharmacogenomics

Interpatient variability in drug response may result from genetically determined differences in metabolism, distribution, and target proteins of drugs. *Pharmacogenetics* is the study of genetic variations that lead to interpatient variations in drug response. This concept is often used interchangeably with pharmacogenomics. In the strictest sense, pharmacogenetics refers to monogenetic variants in drug response while *pharmacogenomics* refers to the entire spectrum of genes that interacts to determine drug safety and efficacy. The goals of these two areas of study are to optimize drug therapy and limit drug toxicity based on an individual's genetic profile. Information gained from studies in these areas will enable clinicians to use genetic tests to select a drug, drug dose, and treatment duration that will have the greatest likelihood for achieving therapeutic outcomes with the least potential for adverse effects in a given patient based on DNA profiles. Much work has already been done in the area of cancer treatment, and information is emerging in the areas of cardiology, neurology, and infectious disease.

Genetic variations commonly occur either as rare defects or polymorphisms. Rare mutations occur in less than 1% of the population while polymorphisms occur in at least 1% of humans. To date, polymorphisms in drug-metabolizing enzymes are the most documented examples of genetic variants that result in altered drug response and toxicity. We will briefly discuss two examples of polymorphic metabolizing enzymes and corresponding drugs whose plasma concentrations and pharmacologic effect may be altered as a result of genetic variation: CYP2C9 and warfarin, and CYP2C19 and clopidogrel.

CYP2C9 is a polymorphic isoenzyme that metabolizes warfarin, phenytoin, and tolbutamide. The S-isomer of warfarin is metabolized by this isoenzyme, and genetic alterations can result in significant reductions in clearance necessitating substantial dose reductions. On the other hand, ultrarapid metabolizers of CYP2C9 require higher doses of warfarin.

Another factor to consider with warfarin metabolism is its target enzyme vitamin K oxidoreductase or VKOR. Warfarin inhibits VKOR, thereby preventing carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X. Genetic alterations in VKOR can result in rare cases of warfarin resistance in which carriers of these mutations require extremely high warfarin doses, or actually may cause a lack of response to warfarin at any dose. Specifically, the VKORC1 genotype in combination with CYP2C0 genotype explains approximately 30% of the interpatient variability in warfarin doses commonly encountered in clinical practice.

Patients who are intermediate metabolizers or poor metabolizers of CYP2C19 may experience a reduced response to clopidogrel and potentially require higher doses or alternative antiplatelet therapy for adequate clinical outcomes. The reason is that clopidogrel is a pro-drug that must undergo conversion via CYP2C19 to its active form.

There are many other examples of differences in response to drugs and adverse drug reactions due to variation in a patient's genetic sequence. These sequence variations can affect enzymes responsible for drug metabolism, drug targets, and drug transporters, all of which will lead to deviation in absorption, distribution, metabolism, and elimination. With isoniazid, for example, there are two distinct subsets of the population with differences in isoniazid elimination (**Figure 11-2**). The elimination of isoniazid is said to exhibit a bimodal pattern. This difference in clearance is caused by genetically controlled differences in hepatic microsomal enzyme production. Likewise, genetic differences in drug elimination also have been observed for hydralazine, warfarin, and phenylbutazone. Polymorphism has been observed in some patients associated with decreased expression of P-glycoprotein (a drug transporter in the duodenum). In these patients, the bioavailability of P-glycoprotein substrates, such as digoxin, is greatly increased; therefore, a decrease in dose may be required.[1]

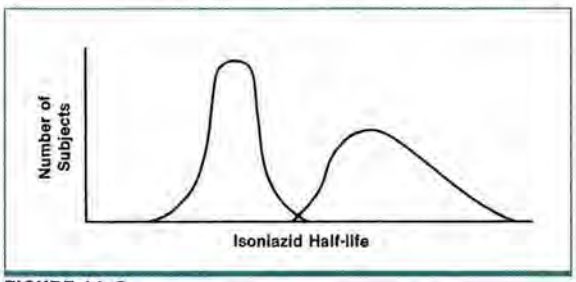

FIGURE 11-2.
Bimodal distribution for isoniazid half-life.

Many variants have also been observed in the cytochrome P450 enzyme system. These variations can cause different responses to drugs metabolized by the CYP450 enzyme system. For example, poor CYP2D6 metabolizers have been found to have elevated fluoxetine levels, and poor CYP2C19 metabolizers were found to have an increased incidence of fluoxetine adverse effects.[2]

Pharmacogenomic research is still in progress. Many sequence variations have currently been observed, but there are countless polymorphisms left to be discovered. Currently, more than 100 drugs contain references to pharmacogenetic information in their approved labeling, and guidelines for the use of genetic information in drug prescribing are beginning to emerge, including those from the Clinical Pharmacogenetics Implementation Consortium. These guidelines are available through the Pharmacogenomics Knowledge Base website (www.PharmGKB.org).

Obesity

Obesity alters drug pharmacokinetics. Because obesity is common in our society, it is an important source of pharmacokinetic variation. With obesity, the ratio of body fat to lean tissue is greater than in non-obese patients. Fat tissue contains less water than lean tissue, so the amount of body water per kilogram of total body weight is less in the obese person than in the non-obese person.

For some drugs, alterations in body makeup that accompany obesity require changes in drug dosages. Drugs that are lipophilic (such as thiopental) and distribute well into fat tissues must often be given in larger doses to achieve the desired effects. Drugs that distribute primarily in extracellular fluids (such as the aminoglycosides) may be given in higher absolute doses to the obese person, but the overall milligram per kilogram dose will be lower. The morbidly obese person who is twice ideal

body weight will have an aminoglycoside volume of distribution that is approximately 1.4 times greater than a person of ideal body weight.[3]

Other Factors

Many other factors may affect drug pharmacokinetics, including pregnancy and drug interactions. Specific changes in pharmacokinetics during pregnancy include increased renal drug clearance, alterations in volume of distribution, and changes in plasma protein binding. Another example of an effect on pharmacokinetics is the histamine-2 blocker, cimetidine, which inhibits the hepatic enzymes that metabolize theophylline, thereby decreasing theophylline clearance. When evaluating drug pharmacokinetics in an individual patient, the clinician must consider the many factors that may cause variations from the expected results.

Potential Sources of Error in the Collection and Assay of Biologic Samples

Pharmacokinetic calculations depend greatly on the validity of the reported drug concentration from a biologic sample (e.g., blood, serum, or plasma). Using incorrect concentration values to calculate dosages can result in subtherapeutic or suprathera-peutic (i.e., toxic) drug concentrations. Inaccurate concentration values can result from incorrect drug sampling or assay procedures. To ensure that drug concentrations are valid, several factors should be considered:

- proper laboratory sample collection and handling,
- physiochemical factors affecting assay accuracy,
- proper laboratory instrument calibration and controls check, and
- proper drug administration and sample timing.

Sample Collection and Handling

To measure drug concentrations, whole blood is usually collected in a blood collection tube called a *serum separator tube* (SST). The SST contains a gel barrier that separates the fluid portion of blood from the solid portion. After collection, the blood is first allowed to clot, which takes approximately 30 minutes, and is then centrifuged for at least 15 minutes to separate the solid components of the blood (blood cells, fibrin, fibrinogen, etc.) from the fluid component. This fluid component is called *serum*. If whole blood is centrifuged before it clots, then only the blood cells are separated from the fluid component, which is called *plasma* (**Figure 11-3**).

Most assays of therapeutically monitored drugs are performed on serum, hence the term *serum drug concentration*. However, the operations manual for specific assay instruments often indicate whether a particular drug may be tested using plasma or serum. Most instruments allow the use of either serum or plasma.

The assay should be performed within 24 hours of sample collection. If this is not possible, refrig-erate the sample (at 2–6°C) until the assay can be performed.

If plastic or glass SSTs are used, it is important to ensure that the drug to be assayed is not affected (i.e., absorbed or adsorbed) by the polymeric gel barrier used to separate the plasma from the cells. The composition of this barrier depends on the brand of SST used. The barriers are usually made of

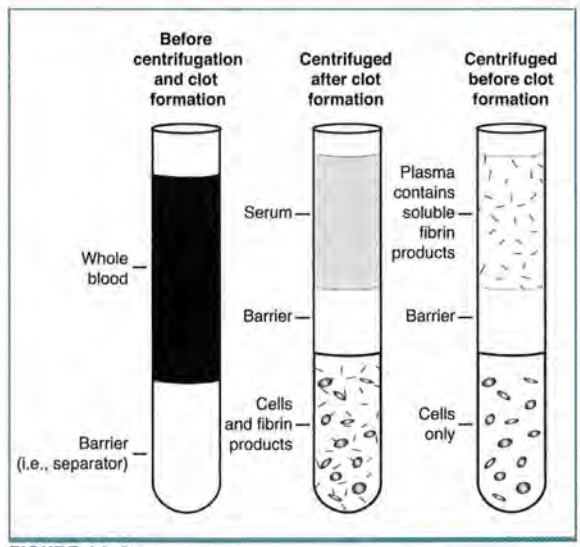

FIGURE 11-3.
Blood products.

acrylic, silicon, or polyester polymers, and although they are generally chemically inert, they can absorb or adsorb the drug being tested.

The degree of absorption or adsorption depends on the hydrophilicity of the drug, the type of barrier used in the SST, the amount of contact time, and the volume of the plasma sample. For example, decreases ranging from 6 to 64% were reported in measured concentrations of phenytoin, phenobarbital, lidocaine, quinidine, and carbamazepine when plasma was stored in Vacutainer SST collection tubes.[4] Adsorption or absorption of drug by the SST barrier is of particular concern when small sample volumes are used (e.g., in pediatric patients) or prolonged storage times are required.

Physicochemical Factors Affecting Assay Accuracy

Most commercially available drug assay methods are immunoassays that use an antibody specific for binding sites only on the drug to be assayed. Various detection methods, such as fluorescence polarization with instruments such as Abbott Diagnostics' TDX/FLEX/ADX and other instruments, are used to quantitate the amount of drug present. These assays can detect the presence of drug at very low concentrations (i.e., microgram or nanogram amounts).

Several assay-specific factors listed in the assay kit package insert can aid in the clinical interpretation of a plasma drug concentration.

Lower Limit of Drug Detection

The lower limit of drug detection indicates the lowest drug concentration that the assay can reliably report. This is a function of the particular assay instrument and is called *assay sensitivity*. Assay sensitivity is the lowest measurable drug concentration that can be distinguished from zero with 95% confidence. Plasma drug concentrations lower than this concentration should be reported as less than this value.

Clinical Correlate

Use caution when interpreting a serum drug concentration reported as < X (e.g., < 0.5 mg/L). This is not the same value as X, but instead means that the sample has no detectible drug concentration above the assay's lower limit of sensitivity. Consequently, this value could be 0, and it could have been 0 for many hours. One cannot reliably use this value to calculate patient-specific *K* values.

Upper Limit of Drug Detection

The upper limit of drug detection indicates the highest drug concentration that can be accurately measured. Plasma drug concentrations above the upper limit will often be reported as higher than this value. If this occurs, assay parameters can be adjusted to increase the dilution volume of the plasma sample, thus allowing higher drug concentrations to be measured.

Assay Interference

Assay interferences are generally categorized as *cross-reactivity* and *physiologic interferences*. The degree of cross-reactivity with other structurally similar compounds is called *assay specificity*. Cross-reactivity is a function of the specificity of the antibody used to bind to the drug. Often, this antibody will also at least partially bind to other compounds that are structurally related to the desired analyte, such as metabolites and chemical analogues of the analyte.

For example, gentamicin assays cross-react with the seldom-used aminoglycoside netilmicin, and amikacin assays cross-react with kanamycin; however, gentamicin and tobramycin assays do not generally cross-react. In addition, patients with impaired renal function who are receiving vancomycin have been shown to accumulate a vancomycin metabolite called *vancomycin crystalline degrada-*

tion product 1 (CDP-1). CDP-1 can cross-react with older assays for vancomycin; however, many newer assay methodologies have reduced this assay interference to an acceptable amount. Clinicians must still be aware of this potential for cross-reactivity. Physiologic substances in the patient's sample may also interfere with the assay. Examples include excess amounts of bilirubin, hemoglobin (i.e., hemolyzed sample), protein, and triglycerides. Plasma drug concentrations are usually not affected by such interferences.

Clinical Correlate

Ask your laboratory's clinical chemistry department for copies of the assay kit package inserts for all drugs that they assay in-house. These inserts will provide useful information, such as the upper and lower limits of assay sensitivity, as well as interfering and cross-reacting substances.

Instrument Calibration and Controls Check

Each drug assay should be calibrated to establish a linear relationship between drug concentration and the instrument's detection method. Calibration of the assay is an automatic process of measuring and plotting different known drug concentrations (i.e., calibrators) based on the instrument's method of detection and measurement. Most assay instruments use some type of spectrophotometric measurement unit, such as fluorescence polarization with Abbott's TDX instrument. **Figure 11-4** is a plot of drug concentration versus the instrument's detection measure (polarization), showing the linear relationship between concentration and polarization. Note that the calibration curve is not linear at very high and very low drug concentrations.

Once this calibration plot or curve is stored in the instrument's software, other unknown drug concentrations (i.e., patient samples) can be accurately determined from this plot. As a quality control check, at least two different known concentrations (control values) should be tested for each drug assay per working shift. If these control values are out of range, as defined per individual laboratory standards, then this assay should be recalibrated and measurement of the patient's plasma drug concentration repeated.

Drug Administration and Sample Timing

To accurately assess drug concentration data and make dosing recommendations, it is important to be aware of administration and sampling factors that may affect the reported drug concentrations. First, drug administration times should be documented, noting any deviations from the recommended dosing schedule. Second, sampling times should be carefully noted so that adjustments can be made in dosage calculations if necessary. Third, it is important to note any other medications the patient is receiving. Occasionally, a patient's sample will contain two drugs, one of which can inactivate the other, particularly if both drugs are infused concomitantly, the sample is taken while the interfering drug is infusing, or a sample containing both drugs is stored at room temperature for a prolonged period.

A good example is the *in vitro* inactivation of the aminoglycosides by penicillins. Cephalosporins have not been shown to inactivate aminoglycosides.[5] Penicillins and aminoglycosides form a chemical complex that is not detected by commercially avail-

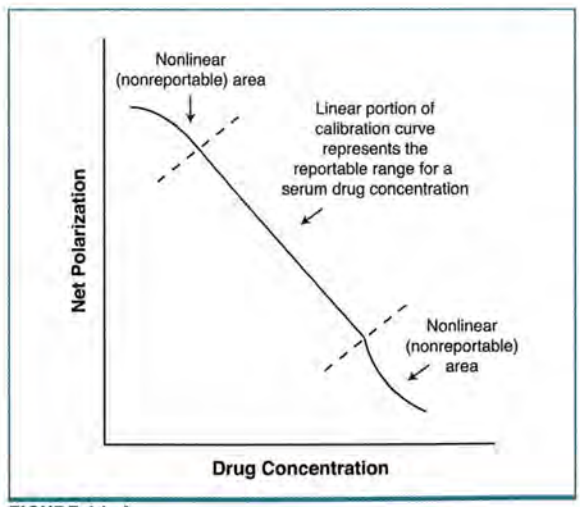

FIGURE 11-4.
Drug concentration versus net polarization.

able drug assays.[6] This *in vitro* inactivation results in a falsely low plasma drug concentration report, which can in turn result in an unnecessary dosage increase. Quantitatively, the aminoglycoside concentration can decline to less than 10% of its original concentration within 24 hours of the beginning of this reaction. These reactions are time and temperature dependent. Refrigerating the sample slows the inactivation process, and freezing the sample stops it completely. To avoid the inactivation process, it is important to adjust the administration times to avoid concomitant infusions of aminoglycosides and penicillins. Drawing a plasma aminoglycoside concentration during infusion of the penicillin should be avoided as well.

Clinical Correlate

When assaying the concentration of an aminoglycoside from a patient who is concomitantly receiving a penicillin, the laboratory must perform the assay immediately or freeze the sample. Freezing the sample instantly stops the *in vitro* inactivation of the aminoglycoside by the penicillin, whereas refrigerating the sample only slows down this degradation reaction. If the assay is not performed immediately, the aminoglycoside level from the assay will be lower than the patient's actual serum aminoglycoside level.

Model-Independent Relationships

Until now, we have used a major assumption in constructing models for drug pharmacokinetics: that drug clearance remains constant with any size dose. Drug clearance remains constant for small or large doses when drug elimination processes are first order (as described in previous lessons). With a first-order elimination process, as the dose of drug increases, the plasma concentrations observed and the area under the plasma drug concentration versus time curve (AUC) increase proportionally. That is, if the dose is doubled, the plasma concentration and AUC also double.

Throughout this self-instructional course, we have emphasized the mathematical relationships of specific pharmacokinetic compartmental models (e.g., one- or two-compartment model after an intravenous bolus or oral dose administration). This lesson reviews several pharmacokinetic parameters that are derived without the assumption of a specific model.

The primary purpose of rigorous pharmacokinetic data analysis, compartmental or model-independent, is to determine the pharmacokinetic parameters useful in dosing drugs for patients. Consequently, multiple plasma drug concentrations are obtained at specific time points in healthy and diseased persons to assess a drug's population pharmacokinetic parameters. In clinical practice, it may be difficult to obtain multiple plasma samples after the first dose to determine a patient's pharmacokinetic parameters. Consequently, clinicians use population parameters from the literature to make individual patient dosage calculations.

Model-independent pharmacokinetic data analysis provides the opportunity to obtain pharmacokinetic values that do not depend on a compartmental model. Total body clearance, mean residence time (MRT), volume of distribution at steady state, and formation clearance are four of the most frequently used model-independent parameters and are the focus of this section.

The use of model-independent data analysis techniques to generate model-independent parameters offers several advantages over traditional compartmental approaches. First, it is not necessary to assume a compartmental model. Many drugs possess complex distribution patterns requiring two, three, or more exponential terms to describe their elimination. As the number of exponential terms increases, a compartmental analysis requires more intensive blood sampling and rigorous data calculations. Second, several drugs (e.g., gentamicin) can be described by one, two, or more distribution compartments, depending on the characteristics of the patients evaluated or the aggressiveness of the blood sampling. Therefore, a compartmental approach would require that pharmacokinetic parameters be obtained for each distribution

pattern, making it difficult to compare one data set to another. Third, calculations are generally easier with model-independent relationships and do not require a computer with sophisticated software.

One drawback of using model-independent parameters is the inability to visualize or predict plasma concentration versus time profiles. This may result in the loss of specific information that provides important insight regarding drug disposition.

Like compartmental pharmacokinetic data analysis, the main purpose of assessing plasma concentration versus time data with model-independent relationships is to determine useful pharmacokinetic parameters. These parameters are usually, but not always, obtained from serial plasma concentration determinations after a single intravenous bolus or oral dose of a drug.

In practice, total body clearance and apparent volume of distribution are the two most important pharmacokinetic parameters because they facilitate the calculation of maintenance and loading dose regimens, respectively. Understanding the effect that disease, altered physiologic state, or drug–drug interaction may have on these pharmacokinetic parameters is important in applying these principles to clinical practice. AUC and area under the first moment curve (AUMC) are two tools used to calculate most model-independent parameters. AUC and AUMC are discussed in the next section.

Total Body Clearance

Total body clearance (Cl_t) is the most important pharmacokinetic parameter because it relates the dosing rate of a drug to its steady-state concentration. It is usually used to calculate a maintenance-dosing regimen. An estimate of Cl_t for a drug is usually obtained after a single intravenous bolus dose (**Figure 11-5**). Total body clearance is calculated with the following equation:

$$Cl_t = \frac{X_0}{AUC_{0\rightarrow\infty}}$$

(See **Equation 3-5.**)

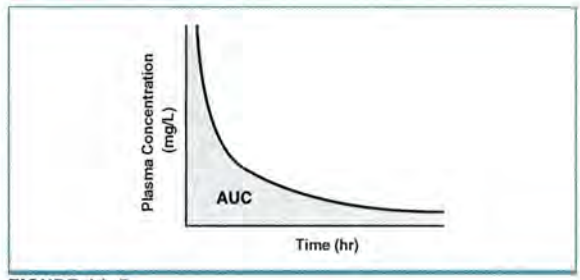

FIGURE 11-5.
Concentration versus time profile after a single intravenous dose. AUC = area under the plasma drug concentration versus time curve.

where:

X_0 = drug dose, and

$AUC_{0\rightarrow\infty}$ = area under the concentration versus time curve from time zero to infinity.

This is a model-independent relationship because calculations do not depend on a specific compartmental model. In other words, we only need the dose and the $AUC_{0\rightarrow\infty}$ to calculate total body clearance. Because the dose is known, a determination of the $AUC_{\rightarrow\infty}$ is all that is needed.

As you can see from **Figure 11-6**, the trapezoidal rule applies only to drugs whose clearance is constant with respect to dose and does not apply to drugs whose clearance is nonlinear. Remember, the trapezoidal rule is a model-independent approach used to directly calculate the AUC of the drug from time zero to the time point that coincides with the last measured plasma concentration value (t_{last}). However, because AUC must include all of the area from zero to infinity after a single intravenous bolus dose, an estimate of the area between t_{last} and

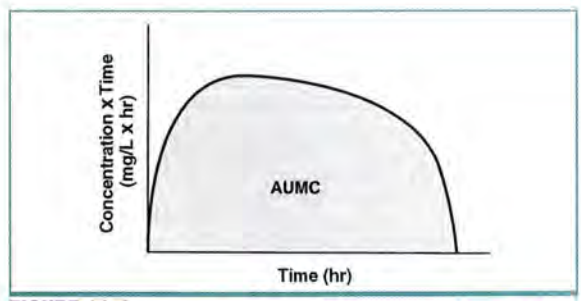

FIGURE 11-6.
Concentration × time versus time curve. AUMC = area under the first moment curve.

infinity is needed. This terminal area can be easily obtained by the following equation:

$$\text{terminal area} = \frac{C_{last}}{\lambda}$$

where:

C_{last} = last measured plasma concentration, and

λ = terminal elimination rate constant.

Two key assumptions in estimating this terminal AUC are that you have a reliable estimate of the terminal elimination rate constant (i.e., slope) and that this value remains constant between t_{last} and infinity.

To determine several model-independent relationships, such as MRT and volume of distribution at steady state, it is important to understand how to calculate the AUMC. The AUMC is the *area under the drug concentration versus time versus time curve*. The AUMC is generated with the AUC data from the concentration versus time profile for a single intravenous bolus dose (see Figure 11-5).

To calculate AUMC after a single intravenous bolus dose of a drug, it is necessary to collect serial drug plasma concentrations over time, determine concentration × time for each plasma concentration, and plot these values versus time on graph paper (see Figure 11-6).

As you can see from Figure 11-6, the shape of the [concentration × time] versus time curve is very different from the drug plasma concentration (C) versus time (t) plot used to calculate AUC. The trapezoidal rule can be used to calculate AUMC. Following a plot as in Figure 11-6, a series of straight lines can be drawn from the concentration × time point to its accompanying time value on the x-axis, forming individual trapezoids (**Figure 11-7**). The area of each trapezoid is calculated with the following equation:

$$\text{area of trapezoid} = \frac{(C_2 \times t_2) + (C_1 \times t_1)}{2}(t_2 - t_1)$$

The sum of all of the trapezoidal areas yields an estimate of the AUMC from time zero to the last observed time point. As in calculating AUC, it is important to obtain AUMC from time zero to infinity.

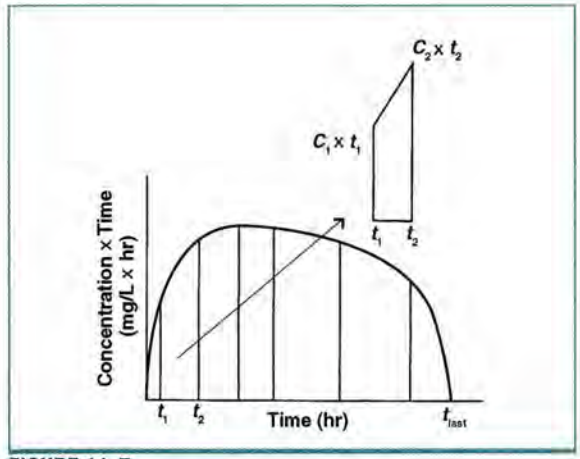

FIGURE 11-7.
Concentration × time versus time curve with trapezoids.

Consequently, the terminal area, which includes the portion of the curve from t_{last} to infinity, must be estimated. Assuming the terminal elimination slope remains constant over this time period, the terminal area is calculated with the following equation:

$$\text{terminal area} = \frac{(C_{last} \times t_{last})}{\lambda} + \frac{C_{last}}{\lambda^2}$$

where:

C_{last} = last observed plasma concentration,

t_{last} = time of the last observed plasma concentration, and

λ = terminal elimination rate constant from the concentration versus time curve. λ is used here (instead of K) to indicate that this represents elimination in a model-independent or noncompartmental analysis.

Mean Residence Time

MRT is defined as the average time intact drug molecules transit or reside in the body. For a population of drug molecules, individual molecules spend different times within the body. Following the principles of statistical probability, specific drug molecules may be eliminated quickly, whereas others may remain in the body much longer. Consequently, a distribution of transit times can be characterized by a mean value. In other words, elimination of a drug can be thought of as a random process. Residence time reflects how long a particular drug molecule

remains or resides in the body. The MRT reflects the overall behavior of a large number of drug molecules. This parameter is not used frequently in clinical practice to monitor patients. However, it is useful when comparing the effect of disease, altered physiologic state, or drug–drug interaction on the pharmacokinetics of a specific drug. MRT can be calculated with the following equation:

$$MRT = \frac{AUMC_{0\to\infty}}{AUC_{0\to\infty}}$$

Volume of Distribution at Steady State

Volume of distribution at steady state (V_{ss}) is a parameter that relates total amount of drug in the body to a particular plasma concentration after a single dose. This parameter is not affected by changes in drug elimination or clearance, making it a useful tool in assessing the effect disease, altered physiologic state, or drug–drug interaction may have on the volume of distribution of a drug. V_{ss} was calculated previously but was only applicable to a drug fitting a two-compartment model. The following equation for V_{ss} does not depend on the model used to describe drug distribution or elimination from the body:

$$V_{ss} = MRT \times Cl_t$$

And since:

$$MRT = \frac{AUMC_{0\to\infty}}{AUC_{0\to\infty}} \text{ and } Cl_t = \frac{X_0}{AUC_{0\to\infty}}$$

then:

$$V_{ss} = \frac{X_0 \times AUMC_{0\to\infty}}{(AUC_{0\to\infty})^2}$$

Formation Clearance

Formation clearance ($Cl_{P\to mX}$) is a model-independent parameter that provides a meaningful estimate of the portion of the total body clearance that is accounted for by production of a specific metabolite. Formation clearance is analogous to systemic and renal clearance of a drug and refers to the formation of metabolites in the course of drug elimination. This parameter is not used to individualize a patient's drug dosing regimen, but is useful when assessing the impact that a specific drug treatment, disease, or altered physiologic state may have on a specific metabolic pathway of a drug. The following equations are used to calculate the formation clearance of a drug:

$$Cl_{P\to m1} = F_{m1}\, Cl_t$$

where:

$Cl_{P\to m1}$ = fractional clearance of the parent drug (P) to form metabolite 1 (m_1),

F_{m1} = fraction of metabolite m_1 formed from a single dose of the parent drug, and

Cl_t = total body clearance.

Or:

$$Cl_{P\to m1} = \left(\frac{m_{1,u}}{X_0}\right)\left(\frac{X_0}{AUC_{0\to\infty}}\right)$$

$$= \frac{m_{1,u}}{AUC_{0\to\infty}}$$

where:

$m_{1,u}$ = amount of metabolite m_1 excreted in the urine.

For example, if a drug is metabolized by three separate enzyme systems, each producing a unique metabolite, what effect would the addition of a known hepatic enzyme inducer have on the individual metabolic pathways? **Figure 11-8** provides a visual perspective of this situation.

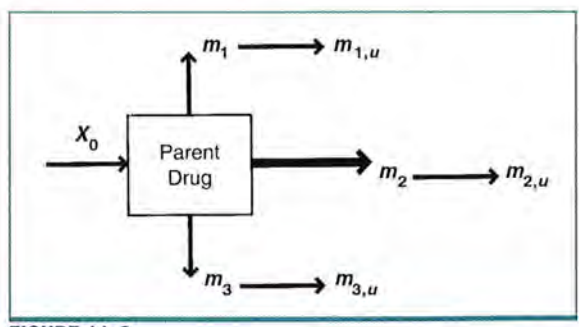

FIGURE 11-8.
Metabolic pathways for a parent drug, where m_1 = metabolite 1, $m_{1,u}$ = amount of m_1 excreted in the urine, m_2 = metabolite 2, $m_{2,u}$ = amount of m_2 excreted in the urine, m_3 = metabolite 3, and $m_{3,u}$ = amount of m_3 excreted in the urine.

To simplify this example, we will assume that systemic clearance equals hepatic clearance, these three metabolic pathways account for 100% of the hepatic clearance of the drug, the metabolite is rapidly secreted unchanged in the urine, and the dose is equal to 100 mg. **Table 11-1** shows the effect of an enzyme inducer on each metabolic pathway portrayed in Figure 11-8 as shown by changes in the percentage of drug dose excreted in the urine for each metabolite and formation clearance.

As Table 11-1 shows, the administration of an enzyme inducer substantially increased the systemic clearance of this drug, from 25 to 75 mL/minute. However, the change in the percentage of the dose excreted as a specific metabolite does not exactly reflect the change in formation clearance values. The percentage of dose excreted in the urine for m_1 was reduced threefold, but no change in the formation clearance was observed. This means that the enzyme inducer had no effect on the enzyme responsible for producing m_1.

On the other hand, treatment with the enzyme inducer produced only a 1.3-fold increase in the percentage of the dose excreted in the urine for m_2 but a fourfold increase in its formation clearance. Finally, the percentage of dose excreted in urine for m_3 was unchanged despite a threefold increase in its formation clearance. Because the formation clearance of a drug to a metabolite reflects more accurately the activity of that specific enzyme, the data would suggest that the enzyme(s) responsible for the formation of m_2 and m_3 was significantly increased by the enzyme inducer, whereas the enzyme(s) responsible for the formation of m_1 was unaffected. The preceding example demonstrates the value of formation clearance versus the more traditional approach of calculating the percentage of a drug dose excreted as a specific metabolite.

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TABLE 11-1. Changes in Formation Clearance of Three Metabolites as a Result of Enzyme Induction

	Metabolite	Percentage of Dose Excreted in Urine	Formation Clearance (mL/minute)
Control (Cl_f = 25 mL/minute)	m_1	20.0	5.0
	m_2	50.0	12.5
	m_3	30.0	7.5
Enzyme induction (Cl_f = 75 mL/minute)	m_1	6.7	5.0
	m_2	63.3	47.5
	m_3	30.0	22.5

REVIEW QUESTIONS

11-1. The proportion of total body weight that is water is lowest in:

A. healthy adults.
B. neonates.
C. elderly.
D. teenagers.

11-2. With dysfunction of the major organs of drug elimination (kidneys and liver), drug clearance, volume of distribution, and drug plasma protein binding may be affected.

A. True
B. False

11-3. For drugs that distribute primarily in extracellular fluid, a dose for an obese person should be calculated using total body weight.

A. True
B. False

11-4. The fluid portion of a sample of whole blood allowed to clot for 30 minutes before centrifugation is called:

A. serum.
B. plasma.
C. serous fluid.
D. citrated blood.

11-5. The fluid portion of whole blood centrifuged before clot formation is called:

A. serum.
B. plasma.
C. serous fluid.
D. citrated blood.

11-6. *Assay cross-reactivity* refers to diminished assay performance caused by:

A. physiologic substances found in some patients' plasma that directly affect the assay itself.
B. structurally related drug compounds or metabolites for which the assay method measures as if they were the desired assay compound.
C. an *in vitro* inactivation of one drug by another drug that is also present in the patient's plasma.
D. none of the above.

Indicate *Yes* or *No* for **Questions 11-7 through 11-10**:

Yes = the accuracy of the drug concentrations is of concern and should be redrawn.

No = the accuracy of the drug concentrations is not of particular concern.

11-7. A gentamicin concentration from a sample stored at controlled room temperature and assayed 24 hours after it was collected from a patient receiving both ampicillin and gentamicin.

A. Yes
B. No

11-8. A plasma tobramycin concentration from a sample stored at controlled room temperature and assayed 24 hours after it was collected from a patient receiving both tobramycin and ceftazidime.

A. Yes
B. No

11-9. A plasma gentamicin concentration from a sample stored in a freezer until assayed 12 hours after it was collected from a patient receiving both ampicillin and gentamicin.

A. Yes

B. No

11-10. A plasma gentamicin concentration from a sample assayed immediately after it was collected from a patient receiving both piperacillin and gentamicin.

A. Yes

B. No

11-11. The trapezoidal rule can be used to calculate AUC for model-independent relationships.

A. True

B. False

11-12. The ratio of $AUMC_{\rightarrow\infty}$ to $AUC_{\rightarrow\infty}$ is called:

A. trapezoidal rule.

B. total body clearance.

C. mean residence time.

D. formation clearance.

11-13. Which statement(s) is/are *false* about the calculation of formation clearance ($Cl_{P\rightarrow mX}$)? Formation clearance can be used to calculate the:

A. clearance rate of individual metabolites of a drug.

B. mean residence time.

C. total body clearance of a drug that has multiple metabolites.

D. A and C.

ANSWERS

11-1. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. The proportion of the body that is water is greatest in the neonate and lowest in the elderly.

11-2. A. CORRECT ANSWER. Major organ dysfunction can affect most pharmacokinetic parameters.

B. *Incorrect answer*

11-3. A. *Incorrect answer*

B. CORRECT ANSWER. The proportion of fat tissue that is extracellular fluid is less than in lean tissue, but the drug will still distribute somewhat in the adipose extracellular fluid.

11-4. A. CORRECT ANSWER

B. *Incorrect answer*. Plasma contains clotting factors.

C. *Incorrect answer*. Serous fluid is a natural body fluid and is not centrifuged to remove cellular components.

D. *Incorrect answer*. Citrated blood contains citrate additives that keep the blood from clotting.

11-5. A. *Incorrect answer*. Serum does not contain clotting factors.

B. CORRECT ANSWER

C. *Incorrect answer*. Serous fluid is a natural body fluid and is not centrifuged to remove cellular components.

D. *Incorrect answer*. Citrated blood contains citrate additives that keep the blood from clotting.

11-6. A. *Incorrect answer*. This is assay interference.

B. CORRECT ANSWER

C. *Incorrect answer*. Assay cross-reactivity does not involve assay measurement of inactivated products that result from some physiochemical process.

D. *Incorrect answer*

11-7. A. CORRECT ANSWER. Ampicillin will inactivate gentamicin *in vitro*.

B. *Incorrect answer*

11-8. A. *Incorrect answer*

B. CORRECT ANSWER. Aminoglycosides are not inactivated by cephalosporins, just penicillins.

11-9. A. *Incorrect answer*

B. CORRECT ANSWER. Freezing this sample will stop inactivation from occurring.

11-10. A. *Incorrect answer*

B. CORRECT ANSWER. Inactivation does not have time to occur if you assay the sample immediately.

11-11. A. CORRECT ANSWER. The trapezoidal rule is a model-independent method for AUC calculation.

B. *Incorrect answer*

11-12. A. *Incorrect answer*. Trapezoidal rule is a method to calculate AUC.

B. *Incorrect answer*. Total body clearance is $X_0/AUC_{0\to\infty}$.

C. CORRECT ANSWER

D. *Incorrect answer*. Formation clearance is a calculation of metabolite clearance.

11-13. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. MRT is calculated using AUC and AUMC.

Discussion Points

D-1. Write a pharmacy protocol to ensure proper serum drug concentration collection and assay.

D-2. Try to get a package insert from your laboratory on any therapeutically monitored drug. Describe the type of information found. Specifically, how are the issues of assay sensitivity, specificity, and cross-reactivity noted?

Practice Set 3

Definitions of symbols and key equations are:

AUC = area under plasma concentration versus time curve

F = fraction of drug reaching systemic circulation

Cl_t = total drug clearance from body = dose/AUC

K_a = absorption rate constant

The following applies to **Questions PS3-1 to PS3-4**. The relative bioavailabilities of two dosage forms (a sustained-release tablet and an oral solution) of oral morphine sulfate are being compared. The following plasma drug concentrations were obtained after 30 mg of each was administered:

	Concentration (mg/L)	
Time after Dose (hours)	Sustained-Release Tablet	Oral Solution
0	0	0
0.5	2.26	19.80
1.0	4.57	18.31
1.5	5.27	15.49
2.0	6.73	12.37
3.0	7.36	9.62
4.0	7.40	6.85
5.0	7.50	5.52
6.0	6.24	3.10
8.0	4.70	1.79
12.0	2.76	1.58

Before proceeding to the questions below, on linear graph paper, plot the plasma drug concentration versus time data for the two formulations.

QUESTIONS

PS3-1. What is the $AUC_{0\text{-}12\ hr}$ for the oral tablet formulation (using the trapezoidal method)?

A. 7.25 (mg/L) × hour
B. 71.25(mg/L) × hour
C. 62.34 (mg/L) × hour
D. 64.51 (mg/L) × hour

PS3-2. What is the $AUC_{0\text{-}12\ hr}$ for the oral solution formulation (using the trapezoidal method)?

A. 6.25 (mg/L) × hour
B. 71.25 (mg/L) × hour
C. 47.42 (mg/L) × hour
D. 64.51 (mg/L) × hour

PS3-3. What are the peak plasma drug concentrations for the oral tablet and oral suspension, respectively?

A. 7.5 and 19.8 mg/L
B. 6.5 and 18.9 mg/L
C. 4.5 and 12.5 mg/L
D. 19.5 and 7.9 mg/L

PS3-4. Which product has greater bioavailability?

A. Oral solution
B. Oral tablet

The following applies to **Question PS3-5**. A single oral dose (500 mg) of a sustained-release procainamide tablet was given, and the following plasma drug concentrations were determined:

Time after Dose (hours)	Plasma Drug Concentration (mg/L)
0	0
0.1	0.60
0.25	1.35
0.5	2.34
0.75	3.05
1.0	3.55
2.0	4.33
4.0	3.89
8.0	2.41
12.0	1.49

Before proceeding to **Question PS3-5**, plot the concentration versus time data on semilog graph paper.

PS3-5. What is the absorption rate constant (K_a) of this formulation (using the method of residuals)?

A. 2.1 hr^{-1}

B. 1.2 hr^{-1}

C. 2.5 hr^{-1}

D. 3.2 hr^{-1}

ANSWERS

PS3-1. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. Using the equation found in Figure 3-10,

$$\frac{(2.26+0)(0.5-0)}{2} = 0.56$$

$$\frac{(4.57+2.26)(1-0.5)}{2} = 1.71$$

$$\frac{(5.27+4.57)(1.5-1)}{2} = 2.46$$

$$\frac{(6.73+5.27)(2-1.5)}{2} = 3.00$$

$$\frac{(7.36+6.73)(3-2)}{2} = 7.05$$

$$\frac{(7.40+7.36)(4-3)}{2} = 7.38$$

$$\frac{(7.50+7.40)(5-4)}{2} = 7.45$$

$$\frac{(6.24+7.50)(6-5)}{2} = 6.87$$

$$\frac{(4.70+6.24)(8-6)}{2} = 10.94$$

$$\frac{(2.76+4.70)(12-8)}{2} = 14.92$$

$$+ \underline{\quad\quad}$$

$$= 62.34 \text{ (mg/L)} \times \text{hr}$$

PS3-2. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. Using the equation found in Figure 3-10,

$$\frac{(0+19.80)(0.5-0)}{2} = 4.95$$

$$\frac{(18.31+19.80)(1-0.5)}{2} = 9.53$$

$$\frac{(15.49+18.31)(1.5-1)}{2} = 8.45$$

$$\frac{(12.37+15.49)(2-1.5)}{2} = 6.97$$

$$\frac{(9.62+12.37)(3-2)}{2} = 10.99$$

$$\frac{(6.85+9.62)(4-3)}{2} = 8.24$$

$$\frac{(5.52+6.85)(5-4)}{2} = 6.18$$

$$\frac{(3.10+5.52)(6-5)}{2} = 4.31$$

$$\frac{(1.79+3.10)(8-6)}{2} = 4.89$$

$$\frac{(1.59+1.79)(12-8)}{2} = 6.74$$

$$+ \underline{\quad\quad}$$

$$= 71.25 \text{ (mg/L)} \times \text{hr}$$

PS3-3. A. CORRECT ANSWER. Observe peak concentration from AUC plot.

B, C, D. *Incorrect answers*

PS3-4. A. CORRECT ANSWER. The oral tablet has a smaller AUC and, therefore, has a lower bioavailability than the oral solution.

B. *Incorrect answer*

PS3-5. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. First, the data points at 4, 8, and 12 hours are on the straight-line terminal portion of the plot and, therefore, are not used to calculate the residual line. Next, the terminal, straight-line portion of the graph is back-extrapolated to the *y*-axis. For each time at which a concentration was actually determined, the concentration corresponding to the back-extrapolated line is noted (extrapolated concentration). The residual is the remainder of the actual concentration subtracted from the extrapolated concentration. The K_a is the negative slope of the natural log of the residual concentration versus time curve. We can choose any two residual points to determine the slope, but it is usually best to select the points most widely separated by time. Therefore,

$$K_a = -\left(\frac{\Delta y}{\Delta x}\right) = \frac{\ln 5.57 - \ln 0.57}{0.1\ \text{hr} - 2.0\ \text{hr}}$$

$$= -\left(\frac{1.72 - (-0.56)}{-1.9\ \text{hr}}\right)$$

$$= 1.20\ \text{hr}^{-1}$$

LESSON 12
Aminoglycosides

This lesson reviews the various renal function assessment equations followed by cases on the appropriate dosing of aminoglycosides.

Renal Function Assessment

The National Kidney Foundation (NKF) stages chronic kidney disease (CKD) into five stages based on glomerular filtration rate (GFR) reported in units of mL/min/1.73 m^2 body surface area (BSA) as shown in **Table 12-1**. Recently, the NKF has recommended the use of the modified diet in renal disease (MDRD) equation (MDRDEQ) to estimate a patient's GFR as a screening tool for early detection of CKD (http://www.kidney.org/professionals/KDOQI/gfr.cfm).

GFR has historically been measured by renal clearance of substances that are 100% excreted via glomerular filtration with no renal tubular reabsorption or secretion, such as inulin clearance, and more recently by renal clearance of radio-labeled ^{125}I-iothalamate, which has now become the gold standard for GFR measurements. However, actual GFR measurements are not commonly done in clinical practice. Instead, clinicians rely on more easily performed estimations of GFR, such as measured creatinine clearance (CrCl), estimated CrCl, and now estimated GFR via the MDRD equation.

CrCl measurement requires a 24-hour collection of urine as shown in the formula below:

$$\text{CrCl} = \frac{UV}{P \times 1440}$$

where:

U = urinary creatinine concentration,

V = volume of urine collected,

P = plasma creatinine concentration (taken at midpoint of urine collection), and

1440 = number of minutes in 24 hours.

Due to the cumbersome nature of direct measurements of either GFR or CrCl, renal function is most commonly estimated with the Cockcroft–Gault creatinine clearance equation (CGEQ) or the $MDRD4_{revised}$ estimated GFR equation. The various versions of the MDRDEQ were developed in a sample that consisted primarily of patients with some degree of CKD and as such may not accurately assess renal function in non-CKD patients.[1] **Table 12-2** shows several versions of both of these equations, including the most commonly used CGEQ using ideal or adjusted body weight.

TABLE 12-1. Stages of Chronic Kidney Disease

Stage 1	Kidney damage with normal or increased GFR	> 90 mL/min/1.73 m²
Stage 2	Kidney damage with mildly decreased GFR	60–89
Stage 3	Moderately decreased GFR	30–59
Stage 4	Severely decreased GFR	15–29
Stage 5	Kidney failure	< 15

GFR, glomerular filtration rate.

Some controversy now exists as to which equation, CGEQ or MDRDEQ, is best to use for renal adjustments of drug doses. Complicating this issue is the recent conversion to new global serum creatinine assay standards that result in a more accurate measurement of creatinine (yielding a value 10% to 20% lower than older assays).[2] Newer measurements can now be reported two places past the decimal (i.e., 1.68 mg/dL). The $MDRD4_{revised}$ equation is the recommended version of the MDRD equation for use with these new assay standards.

Much research has been done to determine which equation is the best; however, it appears that these equations are so dissimilar in their formulation that meaningful comparisons are difficult to perform and are subject to various patient demographic biases, especially age. The CGEQ was derived from a simple general linear multiple regression analysis such that each factor (age, weight, serum creatinine value) in the equation is linearly expressed for the entire tested range of the values. Conversely, the MDRDEQs were correlated using log transformed values and then re-expressed as a *multiplicative linear model* that now contains exponents for the variables of age and serum creatinine and, therefore, produce a geometric relationship across the range of values for each variable tested.

Figure 12-1 is a plot of the age component for both equations, showing that the MDRDEQ calculates a much smaller decline in GFR from age 40 to 80 years than does the CGEQ. Therefore, the MDRDEQ may not predict age-related declines in renal function in the elderly as well as the CGEQ.[3]

TABLE 12-2. Equations Used to Estimate Creatinine Clearance (CrCl) or Glomerular Filtration Rate (GFR)

Cockcroft–Gault estimation of CrCl	
Original form used total weight with no BSA adjustment	TBW(0.85 if female)(140 – age)/(72 × Cr)
Cockcroft–Gault equation most commonly recommended, using IBW or AdjBW*	(IBW or AdjBW*)(0.85 if female)(140 – age)/(72 × Cr)
Modified diet in renal disease (MDRD) equations	
MDRD 6 variable equation with UUN	$198\,(Cr^{-0.858} \times age^{-0.167}) \times BUN^{-0.293} \times UUN^{-0.249}$ [× 1.178 if black and × 0.822 if female]
MDRD 6 variable equation with albumin	$170\,(Cr^{-0.999} \times age^{-0.176}) \times BUN^{-0.170} \times albumin^{-0.318}$ [× 1.178 if black and × 0.822 if female]
MDRD original 4 variable equation	$186\,(Cr^{-1.154} \times age^{-0.203})$ [× 1.212 if black and × 0.742 if female]
MDRD revised 4 variable equation with new creatinine assay standards	$175\,(Cr^{-1.154} \times age^{-0.203})$ [× 1.212 if black and × 0.742 if female]

AdjBW, adjusted body weight; BSA, body surface area; BUN, blood urea nitrogen; Cr, creatinine; IBW, ideal body weight; TBW, total body weight; UUN, urine urea nitrogen.

* AdjBW = IBW + 0.4(TBW – IBW)

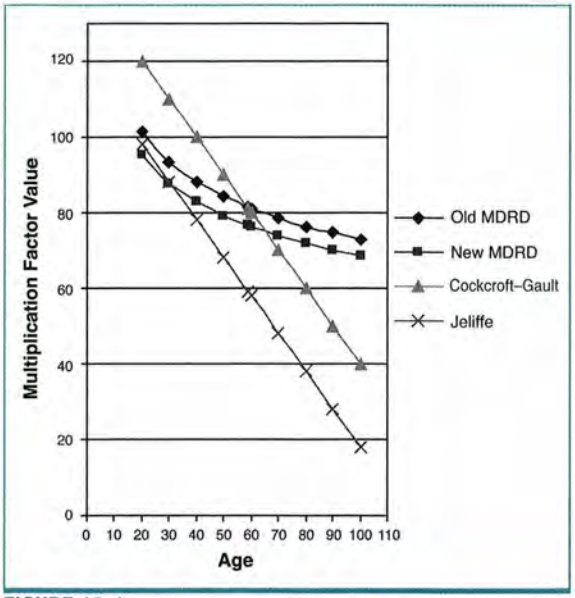

FIGURE 12-1.
A plot of age components of modified diet in renal disease (MDRD) equation and Cockcroft–Gault equation, showing that the MDRD calculates a much smaller decline in GFR from age 40 to 80 years than does the Cockcroft–Gault.

Disregarding this ongoing controversy, it is reasonable to use the CGEQ to adjust drug dosing according to manufacturer's dosing tables that were developed using this same CGEQ. By extension, most pharmacokinetic population values for the elimination rate constant (K) were also developed from regression analyses of drug clearance versus CrCl via the CGEQ, and thus more closely match existing drug dosing tables.

Clinical Correlate

Considerations when using the Cockcroft–Gault equation to adjust drug doses in declining renal function:

1. Use either IBW or an adjusted body weight in the formula and do not make any further BSA adjustments as this formula contains a body size factor of weight/72, which is sufficient to adjust the result for the patient's body size or BSA. Value, in units of mL/min, can now be assumed to approximate a patient's GFR expressed in units of mL/min/1.73 m^2.
2. Most drug manufacturers address dosing adjustments in patients with renal impairment by providing tables showing CrCl versus drug dose, with instructions to adjust dose based on patients' estimated CrCl calculated using the CGEQ.
3. If your laboratory is reporting serum creatinine values that are calibrated to the new IDMS-traceable creatinine assay, be aware that these newer serum creatinine assays will report values to two places past the decimal and will produce values that are lower by as much as 10% to 20% (i.e., ~0.3 mg/dL) compared with older assay methods. This, in turn, will result in a CGEQ estimation of CrCl that is slightly higher than that using the older creatinine calibration techniques. Consequently, a clinical adjustment may be needed when applying a manufacturer's dosing adjustment data based on older creatinine assays to this newer reported creatinine value.

Considerations when using MDRD equations to adjust doses:

1. Note that the MDRD equations are predictors of GFR and not CrCl, and, therefore, their use as replacements of CGEQ estimates for CrCl for drug dosing adjustments will require an individualized assessment of many dosing situations.
2. The MDRD equations were initially validated in patients with chronic kidney disease and may not be as easily generalized to other subsets of patients, including the elderly, as is the more commonly used CGEQ.
3. The MDRD equation may or may not actually be more accurate than the CGEQ for any given patient; however, it can be more easily calculated and reported using routine clinical chemistry analyzer software, as it does not require the patient's weight or height.
4. There is **no** useful conversion factor to convert MDRD GFR to the equivalent CGEQ value because of the differences in the regression models used. Sometimes the MDRD value will be higher and sometimes the CGEQ values will be higher.

Aminoglycoside Dosing

Individualization of aminoglycoside dosing regimens is important to optimize efficacy while minimizing potential toxicity. **Cases 1–4** outline traditional dosing methods of individualized dosing, and **Cases 5** through **7** focus on the extended interval administration of aminoglycosides.

Because the currently available intravenous aminoglycosides (gentamicin, tobramycin, and amikacin) exhibit similar pharmacokinetics, case discussions of one aminoglycoside can be extrapolated to any other. Although amikacin has the same pharmacokinetic profile as other aminoglycosides, it requires doses and target concentrations approximately two to four times as high as the other aminoglycosides.

Several key points should be reviewed before beginning these cases. Aminoglycosides are excreted unchanged by renal glomerular filtration. The elimination, therefore, is proportional to a patient's GFR, which can be estimated by determining CrCl.

Estimation of Elimination Rate Constant (*K*) and Volume of Distribution (*V*) for All Aminoglycosides

Calculate Estimated Creatinine Clearance

Sometimes it is impractical or impossible to collect a 24-hour urine specimen; CrCl must then be estimated from serum creatinine. Although there are several formulas for estimating CrCl, we use the Cockcroft–Gault equation[4]:

$$\text{CrCl}_{\text{male}}\ \text{mL/min} = \frac{(140 - \text{age})\text{IBW}}{72 \times \text{SCr}}$$

(See **Equation 9-1.**)

or

$$\text{CrCl}_{\text{female}}\ \text{mL/min} = \frac{(0.85)(140 - \text{age})\text{IBW}}{72 \times \text{SCr}}$$

where:

CrCl = creatinine clearance (mL/min per 1.73 m^2 BSA),

age = patient's age (years),

IBW = ideal body weight (kilograms) or adjusted body weight (AdjBW) in obese patients, and

SCr = serum creatinine concentration (milligrams per deciliter).

Calculate Ideal Body Weight or Adjusted Body Weight

Because creatinine is produced by muscle metabolism (and not by fat), we must use the patient's IBW or AdjBW when estimating creatinine clearance. *The IBW for adult males can be estimated by:*

IBW = 50 kg + 2.3 kg for each inch over 5 feet in height (See **Equation 9-2.**)

The IBW for adult females is:

IBW = 45.5 kg + 2.3 kg for each inch over 5 feet in height (See **Equation 9-2.**)

In obese patients, the use of total body weight in the CGEQ overestimates creatinine clearance calculations, and the use of IBW underestimates calculation of this variable. Consequently, an AdjBW should be used. If a patient's actual body weight is ≥ 30% above his or her IBW, then the AdjBW must be used to calculate CrCl[5]:

$$\text{AdjBW} = \text{IBW} + 0.4(\text{TBW} - \text{IBW})$$ (See **Equation 9-3.**)

For a patient who weighs less than IBW, the actual body weight would be used in the CGEQ to calculate CrCl.

Clinical Correlate

Close examination of the Cockcroft–Gault equation reveals that serum creatinine values less than 1 mg/dL greatly elevate the calculated CrCl value. This is especially true for elderly patients for whom unrealistically high CrCl values may be calculated using this equation. The elderly often have reduced muscle mass as a fraction of TBW, and so may generate less creatinine than a younger patient of similar weight. In this population, the serum creatinine value may not be an appropriate indicator of the patient's true renal function. It has been recommended to either round the low serum creatinine values up to 1 mg/dL before calculating CrCl, or round the final calculated CrCl value down to ~100 mL/minute or less. Although these recommended adjustments yield more accurate estimations, they still add error to the original CrCl calculation.

Calculate Estimated Elimination Rate and Volume of Distribution

To calculate an initial maintenance dose and dosing interval using traditional dosing methods, we must use population estimates for the elimination rate constant (K) and the volume of distribution (V). Population estimates of K are derived from small studies that correlate an aminoglycoside's clearance (and hence K) to the patient's CrCl (**Figure 12-2**). Creatinine clearance and aminoglycoside clearance are not equal; some amount of aminoglycoside is eliminated by organs other than the kidneys. When creatinine clearance is zero, the aminoglycoside clearance is still approximately 0.014 mL/minute, reflecting this nonrenal clearance and, perhaps, some active tubular secretion.

The equation for the line of best fit through these points can be used to estimate an elimination rate constant (K) for this sample of patients, as shown here:

$$Y = mX + b$$

Or, for example, one commonly used regression equation is:

$$\text{slope } (K) = 0.00293\ (\text{CrCl}) + 0.014$$

where K is the elimination rate constant for aminoglycosides (population estimate). This equation will be used throughout the lesson for all aminoglycosides. These estimates also involve the appropriate calculations of CrCl and IBW. Because many small-sample studies have been done to estimate K and V, there are many different estimates for both. We shall use:

12-1 $K = 0.00293\,(\text{CrCl}) + 0.014$

12-2 $V = 0.24\ \text{L/kg}\,(\text{IBW})$

Clinical Correlate

Approximately 10% of a given aminoglycoside dose distributes into adipose tissue. When calculating aminoglycoside volume of distribution, one can use either IBW or an AdjBW_{AG} formula that reflects this 10% of distribution into adipose tissue as follows:

12-3 $\text{AdjBW}_{AG} = \text{IBW} + 0.1(\text{TBW} - \text{IBW})$

Note that this adjustment is less than that used when calculating AdjBW for use in the creatinine clearance formula. In clinical practice, the AdjBW_{AG} is rarely used.

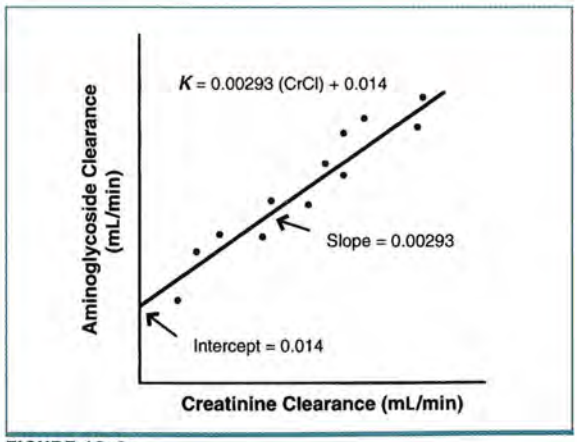

FIGURE 12-2.
Aminoglycoside clearance versus creatinine clearance.

Clinical Correlate

The values for *K* and *V* represent population estimates of the elimination rate and volume of distribution, respectively, based on statistical averages with relatively large standard deviations. For this reason, it is important to obtain peaks and troughs after the initial dosing regimen is established to properly adjust the dosage and dosing interval based on the individual patient's specific pharmacokinetic data.

Clinical Correlate

Some clinicians would use the above *K* and *V* equations as initial population estimates for all aminoglycosides; however, other clinicians may use equations with slightly different numbers based on regression equations derived from similar studies. Additionally, most clinicians will use the same estimates for all aminoglycosides; however, some will use slightly different equations for each aminoglycoside. We will use the above equation for all aminoglycosides as they are all excreted renally via the exact same mechanism.

Desired Aminoglycoside Plasma Concentrations

The traditional ranges for desired aminoglycoside plasma concentrations are a peak of 4–10 mg/L for gentamicin and tobramycin and 15–30 mg/L for amikacin, and a trough of 1–2 mg/L for gentamicin and tobramycin and 5–10 mg/L for amikacin.[5] Attainment of adequate peak concentrations is related to efficacy for some infections, and a low trough concentration may minimize the risk of nephrotoxicity and ototoxicity.

CASE 1

A 66-year-old white female, SG, is hospitalized for lysis of adhesions secondary to previous bowel resection. Before surgery, you are asked to begin this patient on an aminoglycoside. Other pertinent patient data include: height, 5' 8''; weight, 52 kg; and serum creatinine, 1.02 mg/dL.

Problem 1A. Calculate an appropriate aminoglycoside maintenance dose and loading dose, including the most appropriate dosing interval, for patient SG. Assume a desired C_{peak} of 6 mg/L and a C_{trough} of 1 mg/L.

Population values of *K* and *V* for the aminoglycosides should be used to estimate maintenance doses. A patient usually will receive a loading dose over 1 hour when therapy is initiated because a loading dose quickly brings aminoglycoside plasma concentration close to the desired therapeutic concentration. If a loading dose is not given, the patient's aminoglycoside concentration will not reach the desired concentration until steady state is achieved—in five drug half-lives.

Lessons 4 and 5 describe the mathematical models used for various multiple dose, intravenous drug dosing situations. For aminoglycosides, which are usually given intravenously over 30–60 minutes at regular (i.e., intermittent) intervals, Lesson 5 describes the appropriate dosing equation. A quick review of Lessons 4 and 5 may help you understand the derivation of these equations.

Briefly, this equation is arrived at by taking the equation from Lesson 4 for a single intravenous bolus dose and adding the appropriate factors for the following:

- multiple doses,
- simultaneous drug administration and drug elimination,
- drug administration over 30–60 minutes instead of an intravenous bolus, and
- attainment of steady state (for simplicity, 1 hour is assumed for the drug administration time).

The equation is:

$$C_{\text{peak (steady state)}} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

(See **Equation 5-1.**)

where:

$C_{\text{peak(steady state)}}$ = desired peak concentration at steady state (milligrams per liter),

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour),

V = volume of distribution (population estimate for aminoglycosides, in liters),

K = elimination rate constant (population estimate for aminoglycosides, in reciprocal hours),

t = infusion time (hours), and

τ = desired or most appropriate dosing interval (hours).

To solve this equation, we must:

1. Determine creatinine clearance (CrCl).
2. Insert population estimates for V and K.
3. Choose a desired C_{peak}, based on clinical and microbiologic data.
4. Determine our infusion time in hours.
5. Calculate an appropriate dosing interval (τ), as shown below.
6. Determine K_0 (maintenance dose, in milligrams per hour).

To calculate an initial maintenance dose and dosing interval, we use the population estimates of K and V calculated from **Equations 12-1** and **12-2:**

$$K = 0.00293 \text{ hr}^{-1} \times \text{CrCl (in mL/minute)} + 0.014$$

$$V = 0.24 \text{ L/kg} \times \text{IBW}$$

For patient SG, we can calculate the IBW:

$$\text{IBW} = 45.5 + 2.3 \text{ kg per inch over 60 inches}$$

$$= 45.5 + 2.3(8) = 63.9 \text{ kg}$$

However, because SG's actual body weight of 52 kg is less than her IBW, we should use her actual body weight in the calculation of CrCl and in the estimation of her volume of distribution (V).

Estimated CrCl (via the Cockcroft–Gault equation) is:

$$\text{CrCl}_{\text{female}} \text{ mL/min} = \frac{(\text{IBW*})(140-\text{age})0.85}{72 \times \text{SCr}}$$

$$= \frac{(52)(140-66)0.85}{72 \times 1.02}$$

$$= 45.54 \text{ mL/min}$$

**the lesser of IBW or actual body weight*

Furthermore:

$$\text{estimated } K = 0.00293 \text{ (CrCl)} + 0.014$$

$$= 0.00293 \text{ (45)} + 0.014$$

$$= 0.146 \text{ hr}^{-1}$$

$$\text{estimated } T\tfrac{1}{2} = 0.693/K \quad \text{(See } \textbf{Equation 3-3}\text{.)}$$

$$= 0.693/0.146 \text{ hr}^{-1}$$

$$= 4.75 \text{ hours}$$

$$\text{estimated } V = 0.24 \text{ L/kg (weight)}$$

the lesser of IBW or actual weight

$$= (0.24)(52)$$

$$= 12.48 \text{ L, rounded to } 12.5 \text{ L}$$

$$C_{\text{peak (desired)}} = 6 \text{ mg/L}$$

$$C_{\text{trough (desired)}} = 1 \text{ mg/L}$$

Estimation of Best Dosing Interval (τ)

The choice of dosing interval influences the C_{peak} and C_{trough} eventually obtained as well as the magnitude of the fluctuations in C_{peak} and C_{trough}. The equation below is used to determine the most appropriate dosing interval (τ) that will yield the desired C_{peak}

and C_{trough}. As can be seen, this calculation is driven by the patient's elimination rate constant (K) and the C_{peak} and C_{trough} desired:

$$\tau = \frac{1}{-K}(\ln C_{trough\ (desired)} - \ln C_{peak\ (desired)}) + t \quad \textbf{12-4}$$

where t is the duration of the infusion in hours. This equation can be used to evaluate several different C_{peak} and C_{trough} combinations to find an appropriate dosing interval.

Derivation of Above Dosing Interval Equation

The above dosing interval equation comes from a simple rearrangement of the equation for K as shown below.

For a concentration versus time curve (following first-order elimination), the terminal slope equals $-K$ and:

$$-K = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{\ln C_{trough} - \ln C_{peak}}{\tau - t}$$

This equation can be rearranged to easily calculate τ as shown below:

Step 1. Rearrange **Equation 12-4** and then solve for :

$$(-K)(\tau - t) = \ln C_{trough} - \ln C_{peak}$$

Step 2. Divide both sides by $-K$:

$$\tau - t = \frac{\ln C_{trough} - \ln C_{peak}}{-K}$$

Step 3. Transpose t to the right-hand side of the equation:

$$\tau = \frac{\ln C_{trough} - \ln C_{peak}}{-K} + t$$

Step 4. Rearrange:

$$\tau = \frac{1}{-K}(\ln C_{trough} - \ln C_{peak}) + t$$

Step 5. Further rearrange **Step 4** by considering the rule of logarithms:

$$\log a - \log b = \log (a/b)$$

Therefore:

$$\tau = \frac{1}{-K} \ln \left[\frac{\text{trough}}{\text{peak}}\right] + t$$

The equation in either **Steps 4** or **5** can be used to calculate the dosing interval (τ). You may find the equation in **Step 5** easier to enter into a hand-held calculator.

Calculating the dosing interval with both equations (**Steps 4** and **5**) will serve as an added arithmetic check, because both methods should give the same answer.

Clinical Correlate

Some people guess at the best dosing interval and gloat when they get it correct without calculating it. However, if they guess wrong, they will not get the desired trough concentration, and they will have to guess again.

Calculation of Best Dosing Interval (τ) for Patient SG

For patient SG, the calculation of the dosing interval (τ, in hours) proceeds as follows if we want a C_{peak} of 6 mg/L and a C_{trough} of 1 mg/L:

$$\tau = \frac{1}{-K}(\ln C_{trough\ (desired)} - C_{peak\ (desired)}) + t$$

$$= \frac{1}{-0.146}(\ln 1\ \text{mg/L} - \ln 6\ \text{mg/L}) + 1\ \text{hr}$$

$$= (-6.849)(0 - 1.79) + 1\ \text{hr}$$

$$= (-6.849)(-1.79) + 1\ \text{hr}$$

$$= 13.26\ \text{hours}$$

At this point, we know that the best dosing interval to obtain our desired C_{peak} and C_{trough} concentrations is 13.26 hours. In practice, this number would be rounded down to 12 hours.

Calculation of Maintenance Dose for SG

Next, we must determine the maintenance dose to be given at our desired interval of 12 hours. Note that in this example we are calculating the maintenance dose first and will use it to calculate the proper loading dose.

Once K and V have been estimated, the desired C_{peak} and C_{trough} concentrations determined, and τ calculated, these values can be substituted in our general equation and solved for K_0 (maintenance dose):

$$C_{peak\ (steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

(See **Equation 5-1.**)

where:

$C_{peak(steady\ state)}$ = desired peak drug concentration at steady state (milligrams per liter),

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour),

V = volume of distribution (population estimate for aminoglycosides, in liters),

K = elimination rate constant (population estimate for aminoglycosides, in reciprocal hours),

t = duration of infusion (hours), and

τ = desired or most appropriate dosing interval (hours).

Then:

$$6\ mg/L = \frac{K_0(1-e^{-0.146\ hr^{-1}(1\ hr)})}{0.146\ hr^{-1}(12.5)(1-e^{-0.146\ hr^{-1}(12\ hr)})}$$

$$= \frac{K_0(0.1358)}{(1.825)(0.8265)}$$

$$= K_0(0.09)$$

$$66.7\ mg = K_0$$

which would be given over 1 hour for an infusion rate (K_0) of 66.7 mg/hour.

Therefore, patient SG should receive 66.7 mg every 12 hours. In practice, the dose would be rounded to 70 mg every 12 hours. This amount is the initial estimated maintenance dose that would be given until C_{peak} and C_{trough} results are obtained. Because we rounded the dose up from the calculated value of 66.7 to 70 mg, the actual $C_{peak(steady\ state)}$ is slightly higher than our desired value of 6 mg/L. This actual $C_{peak(steady\ state)}$ can be determined via a simple ratio:

$$\text{desired level} \times \frac{\text{actual (rounded) dose}}{\text{calculated dose}} = \text{actual peak}$$

For this patient, the actual $C_{peak(steady\ state)}$ is calculated as follows:

$$6\ mg/L \times \frac{70\ mg}{66.7\ mg} = 6.3\ mg/L$$

Problem 1B. Calculate the C_{trough} concentration expected from the dose of 70 mg every 12 hours for patient SG.

The answer to this problem requires the use of another equation:

$$C = C_0e^{-Kt} \quad \text{(See \textbf{Equation 3-2.})}$$

where:

C = drug concentration at time t,

C_0 = drug concentration at time zero or some earlier time, and

e^{-Kt} = fraction of original or previous concentration remaining at time t.

This general equation can be rewritten to show the calculation of patient SG's C_{trough} concentration after she receives her dose of 70 mg every 12 hours:

$$C_{trough\ (steady\ state)} = C_{peak\ (steady\ state)}e^{-Kt'}$$

(See **Equation 3-2.**)

where $t' = \tau$ – time of infusion (t), or the change in time from the first concentration to the second.

In this case, we are saying that C_{trough} equals C_{peak} multiplied by the fraction of C_{peak} remaining (as described by $e^{-Kt'}$) after elimination has occurred for t hours (i.e., 11 hours). As shown in **Figure 12-3**, because the peak concentration occurs at the end of the 1-hour infusion, t' in this equation is always τ (dosing interval) minus t (duration of infusion).

You should understand how t, τ, and t' differ.

In patient SG's case, the estimated C_{trough} would be:

$$C_{trough\ (steady\ state)} = C_{peak\ (steady\ state)} e^{-Kt'}$$

$$= (6.3\ mg/L)e^{-(0.146\ hr^{-1})(12\ hr - 1\ hr)}$$

$$= (6.3\ mg/L)e^{-(0.146\ hr^{-1})(11\ hr)}$$

$$= (6.3\ mg/L)e^{-1.606}$$

$$= (6.3\ mg/L)(0.200)$$

$$= 1.26\ mg/L;\ round\ to\ 1.3\ mg/L$$

This calculation tells us that 70 mg every 12 hours will give an estimated C_{peak} of 6.3 mg/L and an estimated C_{trough} of 1.3 mg/L. Remember that we actually picked a desired C_{trough} of 1 mg/L, but we also shortened the desired dosing interval from 13.2 to 12 hours, making the estimated C_{trough} higher than the initial desired C_{trough}. If, based on clinical judgment, a lower C_{trough} is desired, the dose can be recalculated with a longer dosing interval, such as 16 hours.

In patient SG's case, if a C_{trough} close to 2 mg/L had been attained, it would have been because we chose a dosing interval shorter than that recommended by our dosing interval calculation. Therefore, we would need to reexamine the rounding of our dosing interval and would probably round it up from 13.2 to 16 or 18 hours.

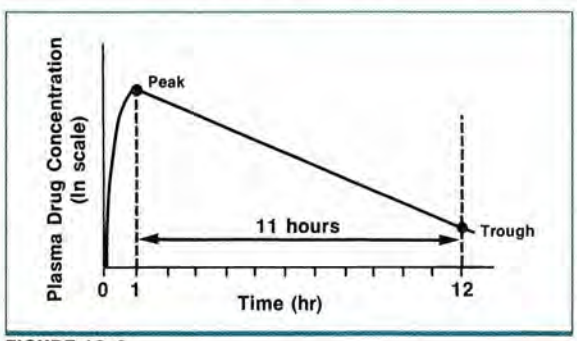

FIGURE 12-3.
Hours of elimination after drug peaks.

CASE 2

In Case 1, we showed how to calculate an appropriate maintenance dose and dosing interval. For this case, we use the data presented in Case 1 and continue treating patient SG.

Problem 2A Calculate an appropriate loading dose to approximate a plasma concentration of 6 mg/L.

There are several methods to calculate a loading dose, and two are presented. Because one method requires estimation of the maintenance dose first, the loading dose is determined after the maintenance dose and dosing interval are calculated. In clinical practice, the loading and maintenance doses would be calculated at the same time.

Like all drugs given at the same maintenance dose via intermittent administration, aminoglycosides will not reach the desired steady-state therapeutic concentration for three (87.5% of steady state) to five (96.9% of steady state) drug half-lives. Therefore, subtherapeutic concentrations may exist for 1–2 days of therapy in patients with longer half-lives. **Figure 12-4A** shows a plasma drug concentration versus time simulation for an aminoglycoside given at the same dose six times.

In Lesson 3, we learned that a patient's drug half-life is dependent on the elimination rate

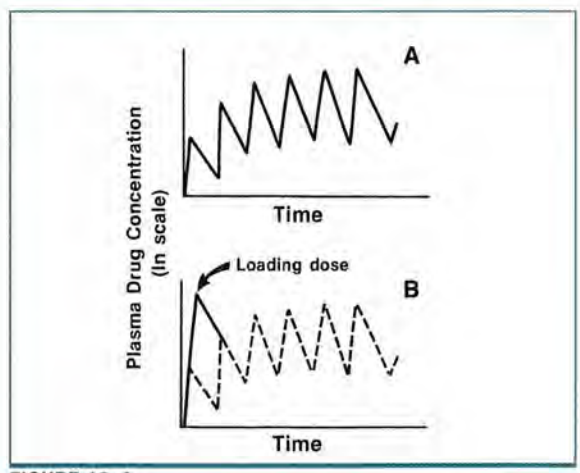

FIGURE 12-4.
A. Drug accumulation to steady state without a loading dose. **B.** Concentration versus time simulation for the same aminoglycoside dose preceded by a loading dose.

constant (K). Mathematically, $T½$ equals $0.693/K$ and, vice versa, K equals $0.693/T½$. Thus, time to reach steady state is dependent on the elimination rate constant (K) for a given patient.

Clinical Correlate

This is an interesting and conflicting concept. Reaching a steady-state drug concentration depends only on the patient's elimination rate (K). Steady state occurs in three to five drug half-lives. The time to steady state cannot be shortened with a loading dose infusion. However, a loading dose infusion can produce a plasma drug concentration approximately equal to the eventual steady-state concentration (see **Figure 12-4B**). That is, a loading dose infusion will quickly bring the patient's drug concentration to a concentration that approximates the concentration at steady state. In addition, any time the dose or dosing interval is changed, it will take another three to five half-lives to reach a new steady-state concentration. After changing a dosing regimen, remember to allow enough time to reach a new steady-state concentration before repeating plasma drug concentrations.

Calculating a Loading Dose

The loading dose infusion can be calculated from the formula for an intermittent infusion not at steady state as shown in Lesson 5:

$$C_{peak\ (steady\ state)} = \frac{K_0}{VK}(1 - e^{-Kt})$$

where:

$C_{peak(steady\ state)}$ = desired peak drug concentration at steady state,

K_0 = loading dose (in mg) to be infused ÷ duration of infusion (in hours),

V = volume of distribution (population estimate, in liters),

K = elimination rate constant (population estimate, in reciprocal hours), and

t = duration of infusion (1 hour).

Clinical Correlate

In Lesson 5, we calculated the loading dose of a drug administered by intravenous push, $X_0 = C_{0(desired)}V$. This equation assumes a rapid infusion of a drug. Because aminoglycosides are infused over 30 minutes to an hour, the equation below must be used to calculate a loading dose to account for the amount of drug eliminated over the infusion period. The term $(1 - e^{-Kt})$ represents the fraction remaining after (t), the time of infusion.

This equation can be rearranged to isolate K_0 on one side of the equation:

$$K_0 = \frac{C_{peak\ (steady\ state)}(VK)}{(1 - e^{-Kt})}$$

Patient SG's loading dose infusion can then be calculated:

6 mg/L (desired peak) can be used instead of actual peak (6.3 mg/L)

$$\text{loading dose} = \frac{(6\ \text{mg/L})(12.5\ \text{L})(0.146\ \text{hr}^{-1})}{(1 - e^{-(0.146\ \text{hr}^{-1})(1\ \text{hr})})}$$

$$= \frac{10.95}{0.1358}$$

$$= 80.6\ \text{mg}$$

By this method, the loading dose infusion can be determined *before* the maintenance dose is calculated, but only with a complicated equation.

Another, easier loading dose formula that requires calculation of the maintenance dose first is shown below:

maintenance dose

12-5 $$\text{loading dose} = \frac{K_0}{(1 - e^{-K\tau})}$$

where:

K_0 = estimated maintenance dose,
$1/(1 - e^{-K\tau})$ = accumulation factor at steady state (see **Equation 4-2**), and
τ = dosing interval at which estimated maintenance dose is given.

With this loading dose formula you are, in essence, multiplying the desired maintenance dose by a factor (the accumulation factor) representing the sum of the fraction of doses that have accumulated at steady state. This factor describes how much the concentration will be increased at steady state.

These two formulas are derivations of each other, as shown below. Begin with our general formula and rearrange it to solve for K_0:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

$$K_0 = \frac{C_{peak(steady\ state)}(VK)}{(1-e^{-Kt})}(1-e^{-K\tau})$$

This corresponds to the circled portion of the next equation.

The first numerator/denominator combination in the above equation is also found in the equation for the loading dose:

$$\text{loading dose} = \frac{C_{peak(steady\ state)}(VK)}{(1-e^{-Kt})}$$

Therefore, the right-hand term of this loading dose equation can be substituted into the general equation for K_0 (**Step 1** below) and then rearranged (**Step 2** below) to then yield our other loading dose formula:

$$\text{Step 1: } K_0 = (\text{loading dose})(1-e^{-K\tau})$$

$$\text{Step 2: (loading dose)} = \frac{K_0}{(1-e^{-K\tau})}$$

For patient SG, the loading dose should be:

$$\text{loading dose} = \frac{K_0}{1-e^{-K\tau}}$$

66.7 mg (actual dose calculated) can be used instead of 70 mg (actual dose given)

$$= \frac{66.7\ \text{mg/hr}}{1-e^{-(0.146\ \text{hr}^{-1})(12\ \text{hr})}}$$

$$= \frac{66.7\ \text{mg/hr}}{0.826}$$

$$= 80.8\ \text{mg}$$

Both loading dose formulas will give approximately the same number. However, some prefer the loading dose equation that requires the maintenance dose to be calculated first because it is simple. Patient SG should receive a loading dose of 80 mg (rounded) followed by a maintenance dose of 70 mg every 12 hours. The 80-mg loading dose should give an approximate C_p of 6 mg/L. Based on the estimated parameters, steady state should be attained in three to five half-lives ($3 \times 4.75 = 14.25$ hours; $5 \times 4.75 = 23.75$ hours). (See **Equation 3-3**.)

CASE 3

To continue with patient SG from Cases 1 and 2, blood was drawn for drug concentration assessment around the fourth dose (i.e., approximately 5 minutes before dose was due and immediately after the 1-hour dose infusion). C_{peak} and C_{trough} were determined as follows:

- 7:55 AM: C_{trough} was 0.4 mg/L (before fourth dose).
- 8–9 AM: 70-mg dose was infused over 1 hour.
- 9 AM: C_{peak} was 4.6 mg/L (after fourth dose).

Although a *peak and trough* was ordered, a *trough and peak* was actually drawn. In this example, the trough level was taken just before the fourth dose was given, and the peak level was obtained just after the fourth dose was given. This procedure is normal and appropriate if the concentrations are at steady state. **Figure 12-5** illustrates that, at steady state, C_{trough} from a trough and peak is equal to the

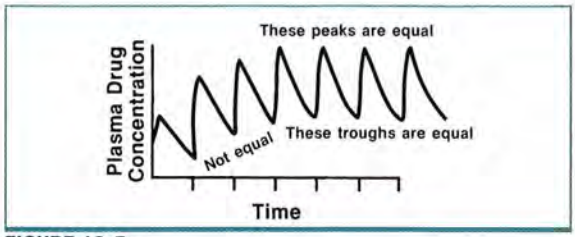

FIGURE 12-5.
Peak and trough concentrations at steady state.

C_{trough} from a peak and trough because all C_{trough} and all C_{peak} values are the same. We know that if we measured a C_{trough} after the C_{peak}, it would equal the C_{trough} before the C_{peak}. This is not true before steady state is reached. In this case, therefore, when a peak and trough is ordered, the literal interpretation would be:

1. Give the infusion from 8 to 9 AM.
2. Draw a sample to determine C_{peak} at approximately 9 AM.
3. Wait until the end of SG's 12-hour dosing interval (approximately 7:55 PM) to draw a sample to determine C_{trough}.

In practice, this method is too cumbersome for pharmacy, nursing, and laboratory staff, so usually a trough and peak is drawn if steady state has been attained.

It is recommended that C_{peak} be measured either at the end of a 1-hour infusion, 30 minutes after the end of a 30-minute infusion, or 1 hour after an intramuscular injection. Infusing aminoglycosides over 1 hour allows simpler pharmacokinetic calculations in that the duration of infusion (t) is 1 hour and the infusion rate (K_0) is simply the dose given. Remember that K_0 is expressed as milligrams per hour. So, if the drug is infused over 30 minutes (0.5 hour), then K_0 = dose (mg)/0.5 (hour).

Clinical Correlate

An actual peak and trough, as opposed to a trough and peak, is sometimes ordered on the first (i.e., not at steady state) dose of a drug to estimate volume of distribution and K in a patient whose drug half-life is quite long. (See Lesson 13, Vancomycin, Case Two, for a case on this.)

Problem 3A. Are patient SG's concentrations of 4.6 mg/L (peak) and 0.4 mg/L (trough) at steady state?

Patient SG's concentrations were determined around the fourth dose, meaning 36 hours after her first dose. To determine whether these serum values are steady-state concentrations, we must use C_{peak} and C_{trough} to calculate SG's actual K and $T½$. These calculations are done in Problem 3C, and the results are 0.222 hr^{-1} for K and 3.12 hours for $T½$. Five half-lives would equal 15.6 hours (3.12 × 5), which is less than the 36 hours elapsed. Therefore, these concentrations are considered to be at steady state. If the drug is not at steady state, the pre-dose C_{trough} would be less than the post-dose C_{trough} and would overestimate K.

Problem 3B. How can you determine when to order drug concentration samples so they are likely to be at steady state?

You want to determine C_{peak} and C_{trough} after the patient is at steady state. Therefore, you must draw blood samples three to five drug half-lives after the first dose. You must estimate the patient's K and $T½$ using population estimates as in Case 1 and then multiply the $T½$ by three to five. As shown in Lesson 4, after three half-lives, concentrations are 87.5% of steady state, whereas after five half-lives, they are 96.9% of steady state. Use judgment when choosing three, four, or five half-lives to calculate time to steady state. Plasma concentration sampling should be scheduled to follow the dose that achieves steady state.

For patient SG, the estimated K and $T½$ (from Case 1, Problem 1A) were 0.146 hr^{-1} and 4.75 hours, respectively. Therefore, steady state would be reached in 23.75 (5 × 4.75) hours. You could then schedule C_{peak} and C_{trough} determinations at the next dose after 24 hours have elapsed.

Clinical Correlate

By calculating the patient's actual elimination rate (K) and volume of distribution (V), pharmacists can more accurately predict patient-specific pharmacokinetic data, thereby optimizing patient care. Once patient-specific parameters are known, it is important not to continue to use population estimates to adjust dosages or dosage intervals.

Problem 3C. Adjust patient SG's dosing regimen, based on C_{peak} and C_{trough} concentrations, to obtain the desired C_{peak} of 6 mg/L and C_{trough} of 1 mg/L.

Adjustment of patient SG's dose involves using the measured drug concentrations to calculate an actual K and V and then substituting these new values for our initial estimates of K and V, in **Equations 3-2, 5-1,** and **12-4,** used in Case 1. The formula for K below comes from a rearrangement of the general equation used to calculate the slope of the natural log of plasma drug concentration versus time line as described in Case 1. Remember that because concentration decreases with time, the slope (and hence, $-K$) is a negative number.

Calculation of SG's Actual Elimination Rate (K)

To calculate K, the equation is:

$$K = -\frac{\ln C_{trough} - \ln C_{peak}}{\tau - t}$$

(See **Equation 3-1.**)

where:

- K = elimination rate constant (in reciprocal hours),
- C_{trough} = measured trough concentration (0.4 mg/L),
- C_{peak} = measured peak concentration (4.6 mg/L),
- τ = dosing interval at the time concentrations are obtained (12 hours), and
- t = duration of infusion (1 hour).

Again, remembering a rule of logarithms:

$$\ln a - \ln b = \ln (a/b)$$

we can simplify this equation for hand-held calculators:

$$K = -\frac{\ln \left(\frac{C_{trough}}{C_{peak}} \right)}{\tau - t}$$

This equation version is more calculator-friendly

Either form of this equation may be used to calculate K, as follows:

$$K = -\frac{\ln 0.4 \text{ mg/L} - \ln 4.6 \text{ mg/L}}{12 \text{ hr} - 1 \text{ hr}}$$

$$= -\frac{-0.916 - 1.52}{11}$$

$$= \frac{-2.44}{11}$$

$$= 0.222$$

Therefore, K = 0.222 hr^{-1}, compared to 0.146 hr^{-1}, which was our estimate, or:

$$K = -\frac{\ln \left(\frac{0.4 \text{ mg/L}}{4.6 \text{ mg/L}} \right)}{12 \text{ hr} - 1 \text{ hr}}$$

$$= -\frac{\ln (0.0869)}{11 \text{ hr}}$$

$$= -\frac{-2.442}{11 \text{ hr}}$$

$$= 0.222 \text{ hr}^{-1}$$

Patient SG's actual K of 0.222 hr^{-1} is greater than the estimated value of 0.146 hr^{-1}, so her elimination probably was greater than estimated. Her actual drug half-life ($T½$) is 3.12 hours, shorter than the population-estimated $T½$ of 4.75 hours:

$$T½ = 0.693/K \quad \text{(See Equation 3-3.)}$$

$$= 0.693/0.222 \text{ hr}^{-1}$$

$$= 3.12 \text{ hours}$$

The formula for K above can also be used to calculate the slope, $-K$, for any two points on the natural log of plasma drug concentration versus time line. For instance, suppose that instead of a C_{peak}, patient SG had a concentration measured at 11 AM (2 hours after C_{peak}). This concentration

was 2.95 mg/L. You can still calculate her K value as follows (**Figure 12-6**):

$$K = -\frac{\ln 0.4\ \text{mg/L} - \ln 2.95\ \text{mg/L}}{12\ \text{hr} - 1\ \text{hr} - 2\ \text{hr}}$$

$$= -\frac{-0.916 - 1.0818}{9}$$

$$= -\frac{-1.9978}{9}$$

$$= 0.222$$

Note that this K value is the same as the one calculated with the measured C_{peak} and C_{trough} concentrations.

Calculation of SG's Actual Volume of Distribution (V)

Patient SG's actual volume of distribution (V) is calculated with the equation from Case 1. Use the actual C_{peak} and C_{trough} values, dose, and dosing interval.

$$C_{peak(steady\ state)} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})}$$

This equation can also be rearranged to isolate V on one side of the equation if the reader so prefers, although it is not normally necessary.

$$V = \frac{K_0(1 - e^{-Kt})}{C_{peak(steady\ state)}K(1 - e^{-K\tau})}$$

(See **Equation 5-1.**)

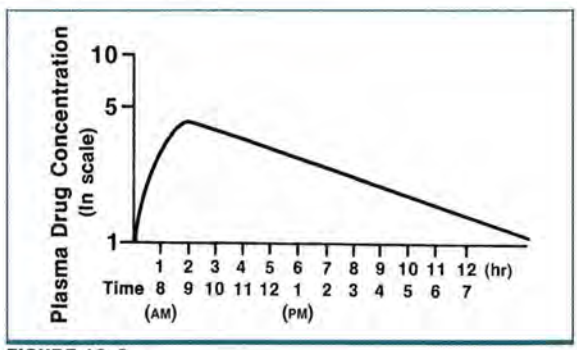

FIGURE 12-6.
K from any two points.

where:

t = the duration of the infusion and

τ = dosing interval at the time concentrations are obtained.

In this case, some of the variables substituted in this equation are different from those used when initially estimating a dose. The changes from Case 1 are shown here in **bold** type:

$C_{peak(steady\ state)}$ = C_{peak} **measured at steady state,**

K_0 = **maintenance dose infused at time C_{peak} and C_{trough} were measured,**

V = **patient's actual** volume of distribution **that you are trying to determine based on C_{peak} and C_{trough} values,**

K = elimination rate constant calculated from patient's C_{peak} and C_{trough} values,

t = duration of infusion (hours), and

τ = **patient's** dosing interval **at time C_{peak} and C_{trough} were measured.**

In patient SG's case, she received a maintenance dose of 70 mg every 12 hours, with subsequent C_{peak} and C_{trough} concentrations of 4.6 and 0.4 mg/L, respectively. Her K value from these concentrations was 0.222 hr^{-1}.

If we substitute these values into the previous equation, we can solve for patient SG's actual V:

$$4.6\ \text{mg/L} = \frac{(70\ \text{mg/hr})(1 - e^{-(0.222\ hr^{-1})(1\ hr)})}{(V)(0.222\ hr^{-1})(1 - e^{-(0.222\ hr^{-1})(12\ hr)})}$$

$$4.6\ \text{mg/L} = \frac{(315)(0.199)}{(V)(0.930)}$$

$$V = 14.7\ \text{L}$$

compared to 12.5 L that we estimated.

Patient SG's V value of 14.7 L (which equals 0.28 L/kg IBW) is larger than estimated and would tend to make her actual C_{peak} and C_{trough} lower than estimated.

Now that we have calculated the patient's actual K and V, we need to recalculate the dose and dosing interval. We must first calculate the new dosing interval (τ) and then calculate the new dose

$$\tau = \frac{1}{-K}(\ln C_{\text{trough (desired)}} - \ln C_{\text{peak (desired)}}) + t$$

where t is the duration of infusion in hours and K is the actual elimination rate calculated from patient's peak and trough values, and *not* the estimated value of 0.146 hr^{-1}. It is important to note that when we calculate our new dosing interval, the values we insert into the equation are our desired levels and not the levels reported by the lab on the dose of 70 mg every 12 hours. Then:

$$\tau = \frac{1}{-0.222\ hr^{-1}}(\ln 1\ mg/L - \ln 6\ mg/L) + 1\ hr$$

$$= (-4.5)(0 - 1.79) + 1\ hr$$

$$= (-4.5)(-1.79) + 1\ hr$$

$$= 9.06\ hr$$

(See **Equation 12-4.**)

This adjusted τ should be compared with our initial τ estimate of 13.26 hours from Case 1, Problem 1A. Because our real τ is shorter than previously estimated, C_{peak} and C_{trough} values less than those predicted also would be expected. In other words, we initially administered a dose every 12 hours when, in actuality, the patient needed a dose every 9 hours.

This calculated dosing interval of 9 hours may be rounded down to 8 hours for ease in scheduling.

Problem 3D. How is patient SG's adjusted maintenance dose now calculated?

Once again, we shall use the general equation from Case 1 and solve for K_0. This time, we shall replace the estimates of K and V with the calculated (actual) values and use the adjusted τ value of 8 hours:

$$C_{\text{peak(steady state)}} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})}$$

(See **Equation 5-1.**)

where:

$C_{\text{peak(steady state)}}$ = desired steady-state C_{peak} (6 mg/L);

K_0 = drug infusion rate (also adjusted maintenance dose you are trying to calculate, in milligrams per hour);

V = actual volume of distribution determined from patient's measured C_{peak} and C_{trough} values, in liters;

K = actual elimination rate constant calculated from patient's measured C_{peak} and C_{trough} values, in reciprocal hours;

t = infusion time, in hours; and

τ = adjusted dosing interval rounded to a practical number.

Strikeovers in the following equation show differences from initial estimated maintenance dose calculations (see Case 1):

$$6\ mg/L = \frac{K_0}{(\cancel{12.5}\ 14.7\ L)(\cancel{0.146}\ 0.222\ hr^{-1})} \left[\frac{(1 - e^{-\cancel{0.146}\ 0.222\ hr^{-1}(1\ hr)})}{(1 - e^{-\cancel{0.146}\ 0.222\ hr^{-1}(\cancel{12}\ 8\ hr)})}\right]$$

$$6\ mg/L = \frac{K_0}{(3.263)}\frac{0.199}{0.831}$$

$$= K_0(0.0732)$$

$$K_0 = 81.9,\ \text{rounded to } 80\ mg$$

If 81.9 mg gives a peak of 6 mg/L, then our rounded dose of 80 mg will give a peak of 5.86 mg/L.

Problem 3E. If we give 80 mg every 8 hours, what will be our steady-state C_{trough}?

If we give 81.9 mg exactly every 9 hours, our C_{trough} would be precisely as desired: 1 mg/L. But because we rounded our dosing interval and adjusted the maintenance dose down to practical numbers, we must calculate the steady-state C_{trough} that will result. Our roundings could make our C_{trough} too high.

This C_{trough} calculation is performed similarly to the one in Case 1, Problem 1B (strikeovers show differences from our initial calculations):

$$C_{trough(steady\ state)} = C_{peak(steady\ state)}e^{-Kt'}$$

(See **Equation 3-2.**)

$$= 5.86\ mg/L\left[e^{-(\cancel{0.146})(0.222\ hr^{-1})(\tau - 1\ hour)}\right]$$

$$= 5.86\ mg/L\left[e^{-(\cancel{0.146})(0.222)(\cancel{11}\ 7)}\right]$$

$$= 5.86\left(e^{-1.554}\right)$$

$$= 5.86\ (0.211)$$

$$= 1.24\ mg/L$$

So, in this case, a dose of 80 mg every 8 hours will give a steady-state C_{trough} of 1.24 mg/L, still well below the usual maximum acceptable trough concentration of 2 mg/L.

CASE 4

Four days later, another set of peak and trough concentrations are obtained. Patient SG has been receiving 80 mg every 8 hours. However, her renal function has declined, as seen by an increase in serum creatinine from 1.02 mg/dL at baseline to 1.71 mg/dL today. C_{peak} and C_{trough} were determined as follows:

- 7:55 AM: C_{trough} was 3.2 mg/L.
- 8–9 AM: an 80-mg dose was infused over 1 hour.
- 9:00 AM: C_{peak} was 9.2 mg/L.

A new adjusted K, τ, V, and maintenance dose (K_0) were calculated using the methods described in Case 3. These values are shown below; see if you obtain the same numbers:

new K = 0.151 hr^{-1},
new $T½$ = 4.6 hours,
new V = 11.1 L,
new τ = 12.6 (rounded to 12 hours),
new maintenance dose (K_0) = 60 mg every 12 hours, and
new trough concentration = 1.1 mg/L.

Problem 4A. Because patient SG's C_{trough} on 80 mg every 8 hours is now too high (3.2 mg/L), how long would you wait before beginning the new dose of 60 mg every 12 hours?

Before switching, you must wait for the patient's C_{trough} to decrease to approximately 1 mg/L. Therefore, the dose should be held for some time before you begin a new lower dose. The formula for calculating the number of hours to hold the dose is:

$$C_{trough\ (steady\ state)(desired)} = C_{trough\ (steady\ state)}\ e^{-Kt'}$$

(See **Equation 3-2.**)

where t' is the amount of time to hold the dose after the end of the 8-hour dosing interval.

This formula is an application of the general formula described in Case 1:

$$C = C_0e^{-Kt} \quad \text{(See Equation 3-2.)}$$

which means:

concentration at a time = previous concentration × fraction of dose remaining

In patient SG's case:

$$1\ mg/L = (3.2\ mg/L)\ e^{-0.151\ hr^{-1}(t')}$$

$$0.312\ mg/L = e^{-0.151(t')}$$

Next, take the natural log of both sides:

$$\ln 0.312 = \ln\left(e^{-0.151(t')}\right)$$

$$-1.163 = -0.151(t')$$

$$7.70\ hours = t'$$

Thus, we should hold patient SG's dose for an additional 7.7 (round to 8) hours after the next C_{trough} time and then begin her new dose. The next C_{trough} time for this patient would be 3:45 PM,

7.75 hours after her last dose (8 AM). The C_{trough} at this time, at steady state, would also be expected to be approximately 3.2 mg/L. We would need to hold the regularly scheduled 4 PM dose for 8 hours, until 12 midnight, at which time we would then begin her new dose of 60 mg every 12 hours.

The calculation of the time to hold a dose can be illustrated (**Figure 12-7**) by plotting patient SG's C_{peak} and C_{trough} values on semilog graph paper and then extending the line connecting them until it reaches our desired C_{trough} of 1 mg/L. You can then count the hours needed to reach this 1-mg/L concentration and hold the dose accordingly.

Another, and often more practical, way to estimate the time to hold a patient's dose is by examining the half-life. By definition, the drug concentration decreases by one-half over each half-life. In the following paragraph, we can then estimate how many drug half-lives to wait for the concentration to approach our desired 1 mg/L.

For patient SG (trough of 3.2 mg/L and $T\frac{1}{2}$ of 4.6 hours), the concentration will drop to 1.6 mg/L (half of 3.2) in one half-life of 4.6 hours and then drop to 0.8 mg/L (half of 1.6) in another 4.6 hours. Therefore, we can hold patient SG's doses for approximately two half-lives (4.6 × 2 = 9.2 hours) before beginning our new dose.

In patient SG's case, another dose was given from 8 to 9 AM, after the C_{trough} of 3.2 was obtained at 7:55 AM. Therefore, her next C_{trough} will occur at approximately 3:45 PM (shortly before the next scheduled dose). We need to hold this dose for an additional 9.2 (round to 9) hours and then begin our new regimen of 60 mg every 12 hours.

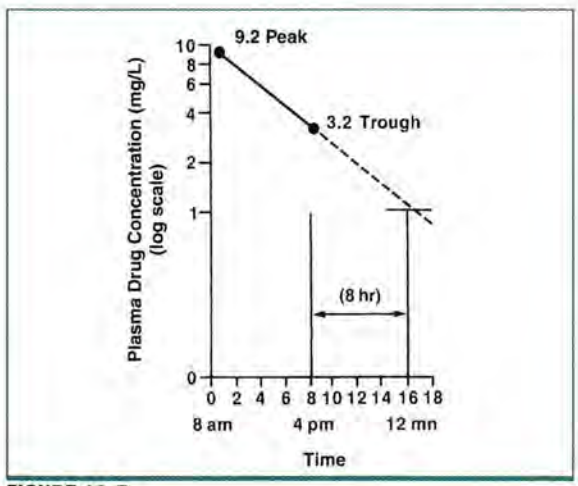

FIGURE 12-7.
Calculation of the time to hold a dose.

Extended-Interval Aminoglycoside Dosing

An alternative method to conventional dosing of aminoglycosides is *extended-interval dosing*—administering large doses over extended intervals (24, 36, or 48 hours) based on the patient's renal function. The theory behind this approach is that administering large doses produces higher peak serum concentrations than achieved with conventional dosing and, thus, increases the peak serum concentration to bacterial minimum inhibitory concentration (MIC) ratio (Peak/MIC).

Additionally, administering drug at an extended interval creates an aminoglycoside-free period that reduces accumulation of aminoglycoside in tissues such as the inner ear and kidney, resulting in decreased drug-related toxicity. It is known that uptake of aminoglycosides by tissues is a saturable process. Administering smaller doses at a more frequent interval does not saturate this process and ultimately leads to higher tissue concentrations than those achieved with extended interval dosing. Thus, this latter dosing method may actually result in less toxicity to the patient. This drug-free interval may also decrease the development of adaptive resistance.

Several characteristics of aminoglycosides as a class enable these drugs to be administered by the extended-interval method. Aminoglycosides demonstrate concentration-dependent bactericidal action such that as the concentration of the drug in the serum increases, the rate and extent of bacterial killing increases. Because of this property, it is suggested that the optimal serum peak aminoglycoside concentration to bacterial MIC ratio is ≥ 10:1. It appears that bactericidal activity occurs in a biphasic fashion; initially, bacteria are killed at a very rapid rate in a concentration-dependent manner. After a time frame of approximately two hours, the rate of bacterial killing declines, which may be due to bacterial adaptive resistance.

Aminoglycosides also exhibit a long post-antibiotic effect (PAE) of approximately 4 to 6 hours. *Post-antibiotic effect* is defined as the amount of time that drug concentration falls below the MIC before regrowth of the bacteria resumes.[6,7,8] PAE is generally thought to increase with high peak concentrations of aminoglycosides.

A third characteristic of aminoglycosides that support extended-interval dosing is a decrease in the development of adaptive resistance. Adaptive resistance results in decreased efficacy of an antibiotic and the emergence of resistant organisms. It is a reversible process if a sufficient drug-free interval between doses is allowed.[9]

Situations in which extended interval aminoglycoside dosing probably should NOT be used include pregnancy, ascites or significant third spacing, hemodynamic instability, unstable renal function (CrCl < 20 mL/min), and burns > 20%.

Numerous methods have been proposed for extended-interval aminoglycoside dosing and monitoring. Several of these methods are presented here.

Method 1

The *2013 Sanford Guide to Antimicrobial Therapy*[5,10] recommends that for gentamicin and tobramycin, the dose in patients with a CrCl > 80 mL/min is 5.1 mg/kg (7 mg/kg for seriously ill patients) every 24 hours, and for amikacin, 15 mg/kg every 24 hours. A patient's IBW is used in these calculations unless actual weight exceeds ideal weight by ≥ 30%. In this case, an AdjBW is used [**Equation 9-3**: AdjBW = IBW + (0.4 × (TBW–IBW).] Goal serum peak concentrations from these doses are 16–24 mcg/mL and 56–64 mcg/mL for gentamicin/tobramycin and amikacin, respectively. Expected trough levels for all three drugs are < 1 mcg/mL. **Table 12-3** lists recommended doses in patients with a reduced CrCl.[10]

Method 2

A second method of extended-interval aminoglycoside dosing consists of administering a dose of 7 mg/kg of gentamicin or tobramycin at an interval based on the patient's CrCl ≥ 60 mL/min, every 24 hours; 40 to 59 mL/min, every 36 hours; 20 to 39 mL/min, every 48 hours. For patients with a CrCl < 20 mL/min, it is recommended to monitor serial serum concentrations and administer a subsequent dose once the serum level is < 1 mcg/mL. With the first dose, a 6- to 14-hour post infusion serum level is measured and plotted on the Hartford nomogram (**Figure 12-8**) to determine if the dosage interval should be altered for future doses.[8]

Method 3

The American Society of Health-System Pharmacists (ASHP) recommends initial doses of 7 mg/kg gentamicin or tobramycin and 15 mg/kg amikacin.[11] This dose is based on the patient's IBW unless their actual weight is 20% over the ideal weight. In this situation, the adjBW should be used. Suggested dosage intervals are as follows: for CrCl > 60 mL/min, every 24 hours; for CrCl 40 to 60 mL/min, a single dose; and for CrCl

TABLE 12-3. Recommended Extended-Interval Dosing in Patients with Declining Renal Function[10]

Creatinine Clearance	Gentamicin/Tobramycin	Amikacin
80–60 mL/min	4 mg/kg every 24 hours	12 mg/kg every 24 hours
60–40 mL/min	3.5 mg/kg every 24 hours	7.5 mg/kg every 24 hours
40–30 mL/min	2.5 mg/kg every 24 hours	4 mg/kg every 24 hours
30–20 mL/min	4 mg/kg every 48 hours	7.5 mg/kg every 48 hours
20–10 mL/min	3 mg/kg every 48 hours	4 mg/kg every 48 hours
< 10 mL/min	2 mg/kg every 72 hours*	3 mg/kg every 72 hours*

*For patients receiving dialysis, these doses should be administered after dialysis.

Source: *The Sanford Guide to Antimicrobial Therapy*, 43rd ed. Sperryville, VA: Antimicrobial Therapy, Inc.; 2013. p. 205.

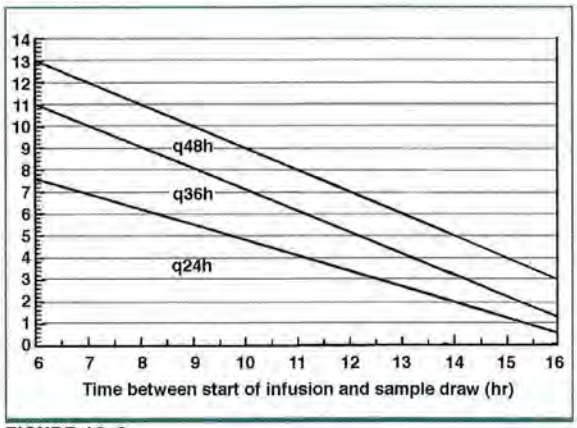

FIGURE 12-8.
Hartford once-daily aminoglycoside adjustment nomogram (gentamicin or tobramycin, 7 mg/kg).

Source: Reproduced with permission from Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother* 1995;39(3):650–5.

< 40 mL/min, a single dose. Obtain a random serum concentration 6 to 12 hours after the first dose and plot the results on an established nomogram such as the Hartford nomogram to determine the appropriate dosage interval. For patients receiving amikacin, divide the serum concentration by 2 and plot this value on the nomogram. The serum concentrations may also be interpreted in light of MIC data if available. Serum levels should be monitored periodically for patients receiving prolonged therapy (> 7 to 10 days) and in patients with unstable renal function. Desired peak serum concentrations with these regimens are a value of 10 to 12 times the MIC of the infecting organism. Desired trough levels are < 1 mcg/mL for gentamicin and tobramycin and < 7 mcg/mL for amikacin.

Method 4

A modification of the ASHP method consists of administering an initial gentamicin or tobramycin dose of 7 mg/kg, or 5 mg/kg for urinary track infections, or 15 mg/kg amikacin followed by measuring a serum concentration 6 to 14 hours after the start of the infusion.[12 (pp. 7–8)] This measured value is then plotted on the Hartford nomogram, and the dosing interval is determined. Because this nomogram is based on a dose of 7 mg/kg, if a smaller dose is administered, the measured serum level should be multiplied by a factor equal to 7 divided by the dose given. For example, if a patient is being treated with the 5 mg/kg dose, 7 divided by 5 equals 1.4, which is then multiplied by the measured serum concentration. This product is plotted on the Hartford nomogram. For amikacin serum concentrations, plot one-half the measured concentration on the nomogram. In situations in which the measured, or adjusted, value falls on one of the three lines, choose the longer interval for administering future doses. Body weight used for these dosage calculations is the patient's actual weight. In cases in which the patient's actual weight is > 20% over their IBW, the AdjBW should be calculated and used in determining the dose. Initial dosing intervals are as follows: for CrCl > 60 mL/min, every 24 hours; for CrCl 40–59 mL/min, every 36 hours; and for CrCl 20–39 mL/min, every 48 hours. If estimated CrCl is < 20 mL/min, do not use extended interval aminoglycoside dosing.

Method 5

An alternative method to those described above consists of using traditional or conventional dosing equations for calculating extended-interval doses. Goal serum peak and trough concentrations utilized should be 20 to 30 mcg/mL and < 1 mcg/mL, respectively, for gentamicin and tobramycin. A minimum dosing interval of 24 hours is selected; increases in this value should be used in cases of declining renal function. The same equations for estimating *K*, *V*, dosing interval, and calculating the maintenance dose as used in traditional dosing methods are then applied.

Method 6

A sixth method is one that may be used in the treatment of patients with cystic fibrosis.[12 (pp.12–14)] An initial dose of 10 mg/kg tobramycin or 20 mg/kg amikacin is administered over a one-hour interval. Dosing weight is as described for Method 4. Serum levels are drawn 1 and 5 hours after the end of the infusion. From these two levels, one may calculate the patient's elimination rate and half-life. For patients with a half-life between 2 and 4 hours,

administer the drug every 24 hours; for serum half-lives > 4 to 6 hours, administer every 36 hours; for half-lives > 6 to 8 hours, give every 48 hours. If calculated half-life is > 8 hours, convert the patient to traditional dosing. If the calculated half-life is < 2 hours, consider changing the patient to tobramycin 7 mg/kg every 12 hours, or amikacin 15 mg/kg every 12 hours. For these latter two regimens, consider monitoring half-life from serum levels to verify that the patient's half-life remains < 2 hours.

CASE 5

JK is a 53-year-old male chronic smoker admitted to the hospital for exacerbation of his chronic obstructive pulmonary disease (COPD). Chest x-ray demonstrates bilateral lower lobe infiltration. Based on his past history, he is suspected of having *Pseudomonas aeruginosa* pneumonia. He is 5' 10'' tall and weighs 170 lbs. His admission serum creatinine is 1.07 mg/dL.

Problem 5A. Calculate an extended-interval dose of tobramycin for this patient according to the *Sanford Guidelines*.

The first step in solving this problem is to determine JK's creatinine clearance. Using the Cockcroft–Gault equation, we can determine this to be 82 mL/min.

$$CrCl = \frac{(140 - age)IBW}{72 \times SCr}$$

$$= \frac{(140 - 53)\,72.73}{72 \times 1.07}$$

$$= 82 \text{ mL/min}$$

Note: If actual weight is less than IBW, use actual weight

Because *Pseudomonas aeruginosa* pneumonia is a serious infection, according to the *Guidelines*, we should administer 7 mg/kg tobramycin times his IBW of 72.73 kg every 24 hours. This results in a dose of 509 mg (round off to 510 mg) every 24 hours.

Problem 5B. According to the *Sanford Guidelines*, in critically ill patients, a peak serum concentration should be drawn on the first dose of the aminoglycoside. The laboratory reports that JK has a peak serum tobramycin level of 23.2 mcg/mL. A serum trough level is also drawn and is reported as 0.8 mcg/mL. Based on these peak and trough levels, should JK's tobramycin dose be changed?

The *Sanford Guidelines* state that serum peak tobramycin levels should be between 16 and 24 mcg/mL and trough levels should be < 1 mcg/mL. JK's values are within these ranges; therefore, no changes in his dose are necessary at this time.

CASE 6

AM is a 32-year-old male with a soft tissue infection in need of gentamicin therapy. He is 6' 2'' tall and weighs 180 lbs. His current serum creatinine is 0.85 mg/dL.

Problem 6A. Calculate an extended interval gentamicin dose for AM using the Hartford nomogram method.

Using the Cockcroft–Gault equation we can determine that AM's creatinine clearance is 123 mL/min.

$$CrCl = \frac{(140 - age)IBW}{72 \times SCr}$$

$$= \frac{(140 - 32)\,82}{72 \times 1.00}$$

$$= 123 \text{ mL/min}$$

notice that a serum creatinine of < 1 (i.e., 0.85) is rounded up to 1.00 for calculation purposes

According to the Hartford nomogram method, he should receive 7 mg/kg every 24 hours:

$$7 \text{ mg/kg} \times 82 \text{ kg} = 574 \text{ mg (round to 570 mg)}$$

Problem 6B. Eleven hours after the beginning of AM's therapy, a serum gentamicin level is drawn and reported as 2.5 mcg/mL. Should AM's gentamicin therapy be adjusted?

Because an 11-hour post-dose level of 2.5 mcg/mL falls within the range for 24-hour dosing, AM's gentamicin therapy does not require adjustment at this time.

Problem 6C. Calculate an extended-interval gentamicin dose for this patient using conventional or traditional dosing equations.

Step 1. Round the CrCl of 123 mL/min to 100 mL/min.

Step 2. Estimate the patient's elimination rate constant.

$$K = 0.00293 \times \text{CrCl} + 0.014$$
$$= 0.00293\ (100\ \text{mL/min}) + 0.014$$
$$= 0.307\ \text{hr}^{-1}$$

Step 3. Estimate the patient's volume of distribution.

$$V = 0.24\ \text{L/kg IBW}$$
$$= 0.24\ \text{L/kg} \times 82\ \text{kg}$$
$$= 19.7\ \text{L}$$

Step 4. Choose a desired steady-state peak serum concentration.

- The recommended range is 20 to 30 mcg/mL.
- For illustration purposes, we will choose 25 mcg/mL.

Step 5. Choose a desired steady-state trough serum concentration.

- The recommended value is < 1 mcg/mL.
- For illustration purposes, we will choose 0.9 mcg/mL.

Step 6. Calculate a desired dosing interval.

- Because this method of dosing is extended interval, a minimum dosing interval of 24 hours should be used. This step is to determine if a patient should receive a dose at a 36- or 48-hour interval.

$$\tau = -1/K \times (\ln \text{trough} - \ln \text{peak}) + t$$
$$= -1/0.307 \times (\ln 0.9 - \ln 25) + 1$$
$$= 12\ \text{hours, which we will round up to 24 hours}$$

Step 7. Calculate a maintenance dose to give the desired peak and trough concentrations.

$$C_{\text{peak(steady state)}} = \frac{K_0(1-e^{-kt})}{VK(1-e^{-k\tau})}$$

$$25\ \text{mcg/mL} = \frac{K_0(1-e^{-0.307(1)})}{19.7\ \text{L} \times 0.307^{-1}(1-e^{-0.307(24)})}$$

$$K_0 = 572\ \text{mg q 24 hours (round to 570 mg)}$$

CASE 7

A 72-year-old female, AC, is involved in a motor vehicle accident resulting in multiple injuries. She undergoes surgical correction of her injuries and postoperatively is admitted to the intensive care unit requiring mechanical ventilation. On hospital day 4, her chest X-ray worsens and sputum cultures isolate *E. coli* sensitive to amikacin. Renal function has remained stable with a serum creatinine of 0.67 mg/dL. She is 5' 4" tall and weighs 130 lbs.

Problem 7A. This case represents an example of a hospital-acquired, or nosocomial, infection. Calculate an appropriate dose of amikacin for AC using the ASHP suggested method.

The first step in solving this problem is to calculate her CrCl.

$$\text{CrCl} = 0.85\frac{(140-\text{age})\text{IBW}}{72 \times \text{SCr}}$$
$$= 0.85\frac{(140-72)54.6}{72 \times 1.00}$$
$$= 44\ \text{mL/min}$$

notice that a serum creatinine of < 1 (i.e., 0.67) is rounded up to 1.00 for calculation purposes

According to the ASHP guidelines, she should receive 15 mg/kg as a single dose with a random serum level drawn 6 to 12 hours after this dose. She receives an initial dose of 15 mg/kg x 54.6 kg = 819 mg (rounded to 820 mg).

Problem 7B. Ten hours after receiving her initial dose, a random amikacin level is 14 mcg/mL. Calculate an appropriate amikacin dosing interval for this patient.

According to the ASHP guidelines, amikacin levels from an extended-interval dose are to be interpreted using an established nomogram. If we use the Hartford nomogram to make this interpretation, it is necessary to divide the reported amikacin level by 2, and this number is then plotted on the nomogram (14 mcg/mL divided by 2 = 7 mcg/mL). Plotting this value on the nomogram demonstrates a dosing interval of every 36 hours. Therefore, this patient should receive amikacin 820 mg every 36 hours.

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Discussion Points

D-1. In Case 1, Problem 1A, suppose SG was admitted to the hospital with gram-negative pneumonia. How would your maintenance dose differ in this patient to achieve a C_{peak} of 8 mg/L and a C_{trough} of 1 mg/L?

D-2. How would your loading dose differ for patient SG in Discussion Point 1 to achieve an approximate peak plasma concentration of 8 mg/L?

D-3. Steady-state peak and trough serum concentrations achieved with the maintenance dose you calculated in Discussion Point 1 were reported by the laboratory as peak = 6.8 mg/L, and trough = 1.8 mg/L. Calculate a new maintenance dose that will give you the desired peak and trough concentrations of 8 mg/L and 1 mg/L, respectively.

D-4. Calculate an extended-interval aminoglycoside dose for SG for a diagnosis of gram-negative pneumonia.

LESSON 13
Vancomycin

In this lesson, Cases 1–4 focus on the antibiotic vancomycin. Before beginning, however, a few key points about vancomycin should be reviewed. Vancomycin is usually administered via intermittent intravenous infusions. For systemic infections, vancomycin is given only by the intravenous route; only this route is considered in this lesson. To minimize the occurrence of an adverse reaction called *red-man syndrome*, vancomycin doses greater than approximately 700 mg are commonly diluted in a larger volume of fluid (i.e., 250 mL) and infused over 2 hours. Vancomycin is the drug of first choice for serious methicillin-resistant staphylococci infections and enterococci (group D streptococcus).

Pharmacokinetically, vancomycin is an example of a two-compartment model, a concept that is discussed in Lesson 6. After intravenous administration, vancomycin displays a pronounced distribution phase (α phase) (**Figure 13-1**) while the drug equilibrates between plasma and tissues. During this initial distribution phase (1–3 hours), plasma drug concentrations are quite high. As the drug distributes throughout the body, the plasma drug concentration declines rapidly over a short period. This biexponential elimination curve for vancomycin is an important consideration especially when evaluating peak plasma vancomycin concentration determinations. It is important not to obtain plasma drug concentrations during this initial distribution phase, as inaccurate pharmacokinetic calculations may result.

Because of vancomycin's strange initial distribution phase, there is some confusion about the therapeutic values for peak and trough concentrations. Older data that suggested peak concentrations of 30–40 mg/L are wrong because they were sampled during this initially high distribution phase. Appropriately sampled peak concentrations were then suggested to be approximately 18–26 mg/L, whereas trough concentrations were suggested to be between 5 and 10 mg/L, except for enterococci, for which vancomycin is only bacteriostatic and required a trough of between 10 and 15 mg/L.

More recently, a consensus review of vancomycin, *Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists*, has presented the evidence for vancomycin toxicity and monitoring.[1] They concluded vancomycin efficacy is best modeled as a total area under the drug concentration-time curve (i.e., concentration-independent killing) versus concentration-dependent older methods of using peak and trough concentrations to measure efficacy. The ratio of the area under the serum drug concentration versus time curve (AUC/MIC) is a common research lab method to measure efficacy. However, most clinical microbiology labs

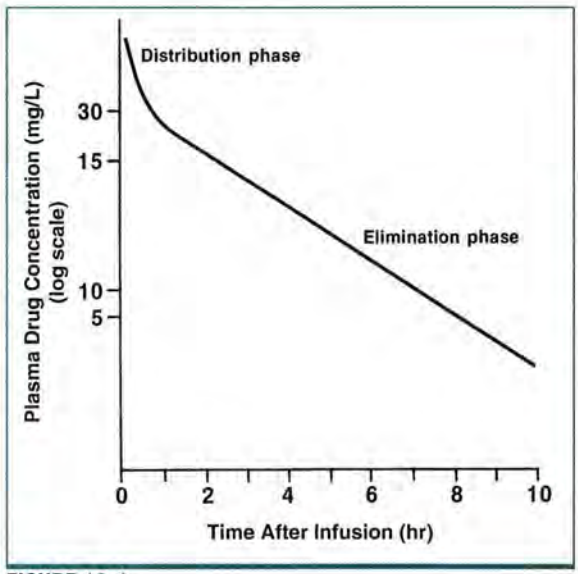

FIGURE 13-1.
Typical plasma concentration versus time curve for vancomycin, demonstrating distribution and elimination phases.

cannot measure AUC/MIC for all pathogens so we rely on vancomycin trough concentrations that can be approximated from AUC/MIC measurements for both efficacy and to decrease development of resistance for organisms with a minimum inhibitory concentration (MIC) < 1. This research has led to a commonly used dosing method based on MIC. MIC < 1 mcg/L requires a vancomycin trough of 10 to 20 mg/L; an MIC of 1.0 requires a trough of 15 to 20 mg/L. They further recommend trough concentrations of 15 to 20 mg/L for complicated infections such as bacteremia, hospital-acquired pneumonia, endocarditis, meningitis, and osteomyelitis. Unfortunately, this consensus paper also presents evidence for increasing nephrotoxicity associated with vancomycin trough concentrations > 15 mg/L, thus creating a dilemma between efficacy and toxicity.

Although routine traditional vancomycin peak and trough level monitoring is often not necessary, measuring both values may be useful to better determine both initial dose, dosing interval, and estimated trough in hemodynamically unstable patients with significant decreases in renal function, in the elderly, and in those patients receiving concomitant nephrotoxic drugs.

Population Estimates for Vancomycin Volume of Distribution (*V*) and Elimination Rate Constant (*K*)

Similar to the aminoglycoside cases in Lesson 12, there are two commonly used population parameters to estimate *V* and *K* that can be used to determine an initial vancomycin dose.

Although vancomycin volume of distribution can vary quite widely, a commonly used average volume of distribution for vancomycin is approximately

13-1 0.9 L/kg total body weight (TBW)

(Note that, unlike the aminoglycosides, it is recommended that TBW be used to calculate the volume of distribution.)

Vancomycin is eliminated almost entirely by glomerular filtration. Therefore, a reduction in renal function results in a decreased vancomycin clearance and an increased half-life. The average vancomycin half-life for a patient with normal renal function is approximately 6 hours ($K = 0.116\ hr^{-1}$). One method of determining population estimates for the elimination rate constant (*K*) based on creatinine clearance (CrCl) is:

13-2 $K = 0.00083\ hr^{-1}$ [CrCl (in mL/minute)] + 0.0044

This equation, developed by Gary Matzke from regression analysis of vancomycin clearance versus creatinine clearance, has units of reciprocal hours, not milliliters per minute. In this type of equation, units are not supposed to cancel out; rather, they assume the units of the correlated value, *K*.

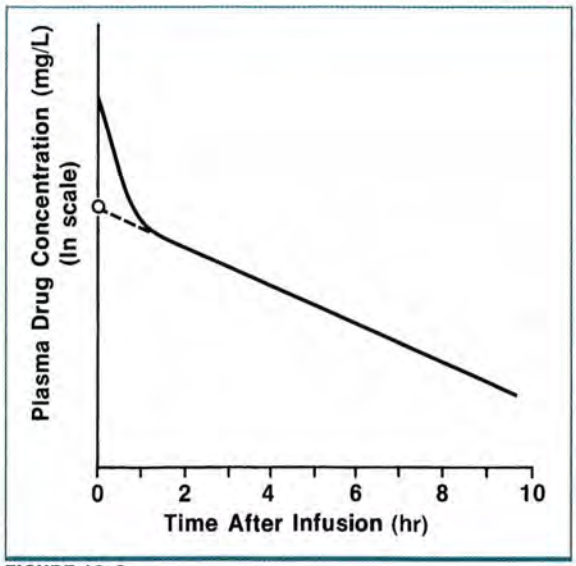

FIGURE 13-2.
Plasma concentration versus time curve for vancomycin, showing simplification with one-compartment model (*dashed line*).

CASE 1

BW, a 42-year-old man, 5' 10'' tall, weighing 90 kg, is admitted to the hospital for a right colectomy because of colon cancer. Initially, he has normal renal function: serum creatinine concentration of 1.00 mg/dL. He subsequently developed a postoperative wound infection, which is treated with surgical drainage and an intravenous cephalosporin.

Culture of the wound fluid reveals methicillin-resistant *Staphylococcus aureus*, with a vancomycin MIC < 1. Pharmacy is then consulted for vancomycin dosing for BW.

Problem 1A. Determine an appropriate dosing regimen of vancomycin to achieve the desired steady-state plasma concentrations of 30 mg/L for the peak (drawn 2 hours after the end of a 2-hour infusion) and approximately 15 mg/L for the trough. How many doses are required to reach steady state?

Several approaches are recommended for the calculation of vancomycin dosages; one relatively simple method is presented here. With this method, we assume that the plasma concentrations during the elimination phase are more valuable for therapeutic drug monitoring than the relatively high, transient vancomycin concentrations of the distribution phase (the first 1–2 hours after the infusion). With this assumption, a one-compartment model can be used to estimate vancomycin dosage or plasma concentrations (**Figure 13-2**). We ignore the distribution phase.

To calculate an initial vancomycin dose, given the desired plasma concentrations, we use population estimates for K and V to solve first for dosing interval and then dose, in a similar fashion to that done for the aminoglycosides, using the first-order one-compartment model equation below:

$K = 0.00083\ \text{hr}^{-1}\ [\text{CrCl (in mL/minute)}] + 0.0044$

$= 0.00083\ (99) + 0.0044$

$= 0.087$, therefore $T\frac{1}{2} = 0.693/0.087$

$= 7.97$ hours

$V = 0.9\ \text{L/kg} \times \text{Total body weight (TBW)}$

$= (0.9)(90)$

$= 81$ liters

rate of drug administration (mg/hr)

% remaining after t hours

13-3 $$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}(e^{-Kt'})$$

τ = desired dosing interval, determined as follows:

13-4 $$\tau = \frac{1}{-K}\left[\ln C_{trough(desired)} - \ln C_{peak(desired)}\right] + t + t'$$

$$= \frac{1}{-0.087\ \text{hr}^{-1}}\left[\ln 15\ \text{mg/L} - \ln 30\ \text{mg/L}\right] + 2\ \text{hr} + (2\ \text{hr})$$

$= 11.97$ hr, rounded up to 12 hr

(See **Equation 5-1** and **Equation 12-4.**)

Note: Additional 2 hr = extra time from end of infusion until level is drawn. Compare to **Equation 12-4.**

where:

$C_{peak(steady\ state)}$ = desired peak concentration 2 hours after infusion,

K_0 = drug infusion rate (dose/infusion time),

t = duration of infusion (usually 2 hours for vancomycin),

K = estimated elimination rate constant (0.087 hr^{-1}),

V = volume of distribution (population estimate of 0.9 L/kg × 90 kg = 81 L),

t' = time between end of infusion and collection of blood sample (2 hours; inclusion of t' is different from the calculation for aminoglycosides [see Lesson 12] because sampling time for vancomycin is actually at least 4 hours after the beginning of the infusion), and

τ = desired dosing interval.

These values are then put into the equation:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-0.087\ hr^{-1}(2\ hr)})}{(81\ L)(0.087\ hr^{-1})(1-e^{-0.087\ hr^{-1}(12\ hr)})} e^{-0.087\ hr^{-1}(2\ hr)}$$

$$30\ mg/L = \frac{K_0(0.16)}{(81\ L)(0.087\ hr^{-1})(0.648)}(0.84)$$

$$K_0 = \frac{(30\ mg/L)(81\ L)(0.087\ hr^{-1})(0.648)}{(0.16)(0.84)}$$

$$\approx 1019\ mg\ vancomycin\ per\ 1\ hr\ (to\ be\ infused\ over\ 2\ hours)$$

Because vancomycin is infused over 2 hours,

$$total\ dose = (1019\ mg/hr)(2\ hr)$$

$$= 2039\ mg\ (round\ to\ 2000\ mg)\ vancomycin\ over\ 2\ hr$$

With this regimen, we can then predict the vancomycin plasma concentration at the end of the dosing interval (trough):

13-5 $$C_{trough} = C_{peak(steady\ state)} e^{-Kt''}$$

where $t'' = \tau - t - t'$
(See **Equation 3-2.**)

where t'' is the difference in time between the two plasma concentrations. In this case, t'' equals τ (12 hours) – t (2 hours) – t' (2 hours), or 8 hours.

$$C_{trough} = 30\ mg/L\ e^{(-0.087\ hr^{-1})(8\ hr)}$$

$$= 30\ mg/L\ (0.499)$$

$$= 14.95\ mg/L$$

So the regimen should result in the desired plasma concentrations of 30 mg/L and approximately 15 mg/L.

The number of doses required to attain steady state can be calculated from the estimated half-life and the dosing interval. Steady state is attained in three to five half-lives. In patient BW's case, we will use three half-lives and our estimated K of 0.087 hr^{-1} in our calculations as follows:

$$time\ to\ steady\ state = 5 \times T_{1/2}$$

$$T_{1/2} = \frac{0.693}{K}$$

$$time\ to\ steady\ state = 5 \times T_{1/2}$$

$$= 5 \times \frac{0.693}{0.087\ hr^{-1}}$$

$$= 5(7.97\ hr)$$

$$= 39.85\ hr$$

If doses are given every 12 hours, then steady state should be achieved by administration of the fourth dose (by the end of the third dosing interval). Remember that doses would be given at 0, 12, 24, and 36 hours.

Problem 1B. To achieve the desired concentrations rapidly, a loading dose can be given. Determine an appropriate loading dose for patient BW. Assume that the loading dose will be a 2-hour intravenous infusion.

To estimate a loading dose, we need to know the volume of distribution and the elimination rate constant. Because we do not know the patient-specific pharmacokinetic values, the population estimates can be used (V of 0.9 L/kg TBW [see **Equation 13-1**] and K of 0.087 hr^{-1} as previously determined [see **Equation 13-2**]). Then the equation as shown in Lesson 5 describing plasma concen-

tration over time with an intravenous infusion is applied. Note that again we ignore the distribution phase and assume that a one-compartment model is adequate (**Figure 13-3**):

$$C_{\text{peak desired}} = \frac{X_0/t}{VK}(1 - e^{-Kt})e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{\text{peak(steady state)}}$ = desired peak plasma concentration 2 hours after infusion,

X_0 = dose (note: $X_0/t = K_0$),

t = duration of infusion (2 hours),

K = 0.087 hr^{-1},

V = 81 L, and

t' = time after end of infusion (2 hours).

Note that the term $e^{-Kt'}$ describes the decline in plasma concentration from the end of the infusion to some later time (2 hours in this example). Then, insertion of the known values gives:

$$30 \text{ mg/L} = \frac{(X_0/2 \text{ hr})(1 - e^{-0.087 \text{ hr}^{-1}(2 \text{ hr})})}{(81 \text{ L})(0.087 \text{ hr}^{-1})} e^{-0.087 \text{ hr}^{-1}(2 \text{ hr})}$$

$$= \frac{(X_0/2 \text{ hr})(0.16)}{(7.05 \text{ L/hr})}(0.84)$$

$$X_0 = \frac{(30 \text{ mg/L})(7.05 \text{ L/hr})(2 \text{ hr})}{(0.84)(0.16)}$$

Note: This 2 is from transposing the 2 in $X_0/2$ component indicating that the loading dose is infused over 2 hours

= 3147 mg vancomycin, which may be rounded to 3000 given over 2 or 3 hours

Clinical Correlate

Note that although the calculated loading dose is 3147 mg, many clinicians would choose to either infuse this over more than 2 hours, or give this loading dose as two doses about 4 to 6 hours apart to minimize potential vancomycin infusion reactions such as red-man syndrome. Also, note how this calculated loading dose compares to the easier method of using 25 to 30 mg/kg TBW.

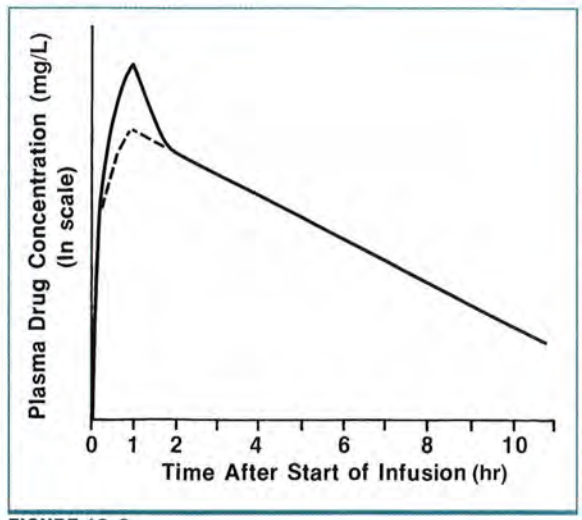

FIGURE 13-3.
Plasma concentrations over time for a loading dose. Dashed line represents simplification to one-compartment model.

Clinical Correlate

Close observation of Figure 13-3 confirms that we are not actually measuring a true peak concentration, as we did for aminoglycosides. We are, rather, measuring a 2-hour postpeak concentration that places this point on the straight-line portion of the terminal elimination phase.

Problem 1C. After administration of the loading dose and seven doses (1500 mg each) at 12-hour intervals, plasma vancomycin concentrations are determined to be 42 mg/L (2 hours after the end of the 2-hour infusion) and 22 mg/L at the end of the dosing interval. Calculate a new dose for BW (this time using actual patient-specific K and V) to attain the original target peak and trough concentrations (30 mg/L and 15 mg/L, respectively).

The information needed to determine a new dosing regimen is the same as described in Problem 1A. However, because we now have data about this specific patient, we no longer have to rely on population estimates. To begin, we should calculate the patient's vancomycin elimination rate constant, half-life, and volume of distribution from the plasma concentrations determined.

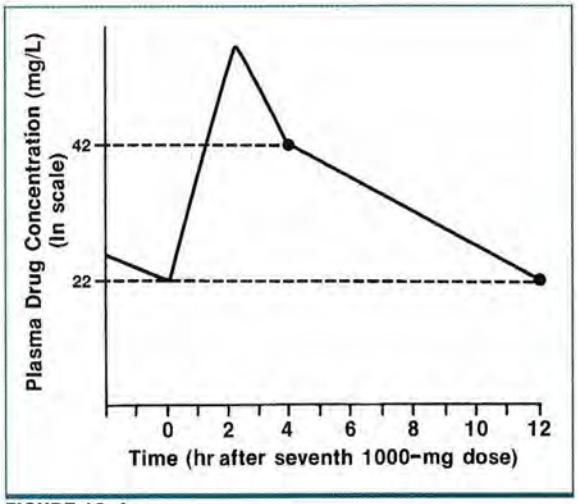

FIGURE 13-4.
Calculation of elimination rate constant given two plasma concentrations (42 mg/L at 2 hours after the infusion and 22 mg/L at 10 hours after the end of a 2-hour infusion).

Calculation of *K*

First, the elimination rate constant (K) is easily calculated from the slope of the plasma drug concentration versus time curve during the elimination phase (**Figure 13-4**) (see Lesson 3):

$$K = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1}$$

$$= -\frac{\ln 22\ \text{mg/L} - \ln 42\ \text{mg/L}}{10\ \text{hr} - 2\ \text{hr}}$$

$$= -\frac{3.09 - 3.73}{8\ \text{hr}}$$

$$= 0.08\ \text{hr}^{-1}$$

(See **Equation 3-1.**)

Clinical Correlate

Be careful when selecting t_2 and t_1. In the above example, if dose one is begun at 8 AM and infused for 2 hours, then the patient would receive the entire dose by 10 AM. The peak plasma level would then be drawn 2 hours later, or 12 noon. Given that the trough concentration will be attained immediately before dose two (given at 8 PM), the total time elapsed between the plasma readings is 8 hours, or ($t_2 - t_1$).

The half-life ($T\frac{1}{2}$) can then be calculated:

$$T\frac{1}{2} = \frac{0.693}{K}$$

$$= \frac{0.693}{0.08\ \text{hr}^{-1}}$$

$$= 8.66\ \text{hr}$$

(See **Equation 3-3.**)

Calculation of *V*

Note that the elimination rate constant is lower, and the half-life is greater than originally estimated. Now the volume of distribution (V) can be estimated with the multiple-dose infusion equation for steady state:

$$C_{\text{peak(steady state)}} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{\text{peak(steady state)}}$ = peak concentration 2 hours after infusion = 42 mg/L,
K_0 = maintenance dose (1500 mg over 2 hours),
t = duration of infusion (2 hours),
t' = time between end of infusion and collection of blood sample (2 hours),
K = elimination rate constant (0.08 hr^{-1}),
V = volume of distribution (to be determined), and
τ = dosing interval (12 hours).

These values are then put into the equation:

$$C_{\text{peak(steady state)}} = \frac{(1500\ \text{mg}/2\ \text{hr})(1 - e^{-0.08\ \text{hr}^{-1}(2\ \text{hr})})}{V(0.08\ \text{hr}^{-1})(1 - e^{-0.08\ \text{hr}^{-1}(12\ \text{hr})})} e^{-0.08\ \text{hr}^{-1}(2\ \text{hr})}$$

$$42\ \text{mg/L} = \frac{(1500\ \text{mg}/2\ \text{hr})(0.148)}{V(0.08\ \text{hr}^{-1})(0.617)}(0.85)$$

Rearranging gives:

$$V = \frac{(1500\ \text{mg/2 hr})(0.148)(0.85)}{(0.08\ \text{hr}^{-1})(0.617)(42\ \text{mg/L})}$$

$$= 45.5\ \text{L or } 0.51\ \text{L/kg}$$

So the original estimate for the volume of distribution was higher than the volume determined with the plasma concentrations.

Calculation of New τ

Before calculating a new maintenance dose, we can first check to see if we need to use a new dosing interval, as follows:

$$\tau_{desired} = \frac{1}{-K}[\ln C_{trough(desired)} - \ln C_{peak(desired)}] + t + t'$$

(See **Equation 13-4.**)

where:

t = duration of infusion (2 hours),

t' = time after end of infusion (2 hours), and

τ = dosing interval, calculated as follows:

$$\tau = \frac{1}{-0.08\ hr^{-1}}(\ln 15\ mg/L - \ln 30\ mg/L) + 2\ hr + 2\ hr$$

$$= \frac{1}{-0.08\ hr^{-1}}(2.7 - 3.4) + 4\ hr$$

$$= 12.66\ hr$$

Therefore, our best new dosing interval is approximately 12 hours.

Calculation of New K_0

$$C_{peak\ (steady\ state)} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})}e^{-Kt'}$$

$$30\ mg/L = \frac{K_0(1 - e^{-0.08\ hr^{-1}(2\ hr)})}{(0.08\ hr^{-1})(45.5\ L)(1 - e^{-0.08\ hr^{-1}(12\ hr)})}e^{-0.08\ hr^{-1}(2\ hr)}$$

$$= \frac{K_0(0.148)}{(0.08\ hr^{-1})(45.5\ L)(0.62)}(0.847)$$

Rearranging gives:

$$K_0 = \frac{(30\ mg/L)(0.08\ hr^{-1})(45.5\ L)(0.62)}{(0.148)(0.847)}$$

$$= (540\ mg/hr)(2\text{-}hr\ infusion)$$

$$= 540\ mg\ for\ 2\ hours = 1080\ mg,$$

which will round to 1000 mg

Resultant C_{peak} and C_{trough} concentrations for a 1000-mg every-12-hour dose would be ~32 mg/L and 14.4 mg/L, respectively.

Clinical Correlate

One can easily see how this tedious, repetitive calculation of dose, dosing interval, and trough concentration can be made much simpler by using various computer and PDA dosing programs, allowing you to try many different combinations.

CASE 2

PS, a 74-year-old woman, 60 kg, 5' 7'' tall, serum creatinine of 2.50 mg/dL, is admitted to the hospital after sustaining multiple traumatic injuries in a motor vehicle accident.

She experiences a spiking fever; gram-positive cocci, resistant to methicillin but susceptible to vancomycin, are subsequently cultured from her blood. Her physician consults the pharmacy for vancomycin dosing and monitoring. A quick clinical assessment of this patient indicates that her renal function is extremely low, meaning her time to steady state would be many days. Estimated pharmacokinetic parameters confirm this assumption: CrCl ~18.7 mL/minute, estimated *K* of 0.02, *V* of 54 liters, *T½* of ~35 hours, and, therefore, a time to steady-state calculation of between 104 hours, using three half-lives, and 173 hours, using five half-lives.

Note that there are two opportunities to calculate patient-specific pharmacokinetic values—after the first dose or after steady state has been achieved. In this case, because the patient has such a long half-life, it is decided to calculate these parameters after the first dose, which allows for subsequent dose adjustments without waiting the many days necessary for steady state to be reached. The reason for calculating this patient's elimination rate constant and volume of distribution is to predict how often a vancomycin dose will be needed, when the next dose should be given, and the size of the next dose.

Problem 2A. Two hours after the end of a 1000-mg loading dose administered over 1 hour, the vancomycin plasma concentration was 29 mg/L; it is 17.5 mg/L at 35 hours after the end of this infusion (**Figure 13-5**). Calculate the vancomycin elimination rate constant, half-life, and volume of distribution in this patient.

First, we calculate the elimination rate constant (K) and half-life ($T½$):

$$K = -\text{slope of natural log of vancomycin concentration versus time plot}$$

$$= -\frac{\ln C_2 - \ln C_1}{t_2 - t_1}$$

$$= -\frac{\ln 17.5 \text{ mg/L} - \ln 29 \text{ mg/L}}{35 \text{ mg} - 2 \text{ hr}}$$

$$= 0.015 \text{ hr}^{-1}$$

(See **Equation 3-1.**)

Clinical Correlate

Remember that the second plasma level was taken 35 hours after the **end of the infusion**, not 35 hours after the first plasma level. Therefore, we must account for the 2 hours that elapsed between the end of the infusion and first plasma level.

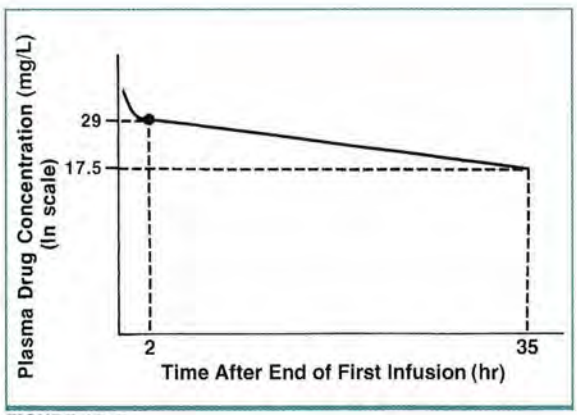

FIGURE 13-5.
Plasma concentrations after loading dose of vancomycin in a patient with renal impairment (29 mg/L at 2 hours and 17.5 mg/L at 35 hours after the end of the infusion).

The half-life in this case can be calculated:

$$T½ = \frac{0.693}{K}$$

$$= \frac{0.693}{0.015 \text{ hr}^{-1}}$$

$$= 46.2 \text{ hr}$$

(See **Equation 3-3.**)

Now the volume of distribution (V) can be estimated, using the simple relationship given below:

$$\text{loading dose} = \text{plasma concentration achieved} \times \text{volume of distribution}$$

By rearranging, we get:

$$V = \frac{\text{loading dose}}{\text{plasma concentration achieved}}$$

$$= \frac{1000 \text{ mg}}{29 \text{ mg/L}}$$

$$= 34.5 \text{ L}$$

Note that the patient's calculated K of 0.015 hr and V of 34.5 L are both lower than our estimated values of 0.02 hr and 54 L, respectively.

Problem 2B. With the information just determined, calculate when the next vancomycin dose should be given and what it should be. Assume that the plasma vancomycin concentration should decline to 12 mg/L before another dose is given and that the plasma concentration desired 2 hours after the infusion is complete is 29 mg/L (i.e., desired C_{peak}).

First, we must know the time needed for the plasma concentration to decline to 12 mg/L. It can easily be calculated from the known plasma concentrations, the elimination rate constant, and the desired trough plasma concentration:

$$C_{trough} = C_{peak}\, e^{-Kt}$$

where:

C_{peak} = observed concentration of 29 mg/L,
K = elimination rate constant (0.015 hr^{-1}), and

t = time between observed concentration of 29 mg/L and trough concentration of 12 mg/L (unknown).

Then:

$$12 \text{ mg/L} = (29 \text{ mg/L})(e^{(-0.015 \text{ hr}^{-1})(t)})$$

To solve for t, we can first take the natural log of each side of the equation:

$$\ln 12 \text{ mg/L} = \ln 29 \text{ mg/L} \; (-0.015 \text{ hr}^{-1})(t)$$

Rearranging gives:

$$t = \frac{\ln 15 \text{ mg/L} - \ln 29 \text{ mg/L}}{-0.015 \text{ hr}^{-1}}$$

$$= 44.6 \text{ hr}$$

Therefore, at approximately **45** hours after the plasma concentration of 29 mg/L is observed (or ~47 hours after the end of the infusion), the next vancomycin dose can be given.

Next, we determine dosing interval and maintenance dose as follows:

$$\tau_{desired} = \frac{1}{-K}[\ln C_{trough(desired)} - \ln C_{peak(desired)}] + t + t'$$

$$= \frac{1}{-0.015 \text{ hr}^{-1}}[\ln 12 \text{ mg/L} - \ln 29 \text{ mg/L}] + (1 \text{ hr} + 2 \text{ hr})$$

$$= \frac{1}{-0.015 \text{ hr}^{-1}}[2.70 - 3.4] + 3 \text{ hr}$$

$$= 45 \text{ hr, rounded up to } 48 \text{ hr}$$

Assume a 1-hour infusion and a 2-hour time to wait before obtaining vancomycin peak concentration

(See **Equation 13-4**.)

The maintenance dose can then be calculated as follows:

$$C_{peak(steady\ state)} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See **Equation 13-3**.)

where:

$C_{peak(steady\ state)}$ = concentration 2 hours after end of infusion,

τ = 48 hours,

t = duration of infusion (1 hour),

t' = time after end of infusion (2 hours),

V = 34.5 L, and

K = 0.015 hr^{-1}.

Rearranging to solve for K_0:

$$K_0 = \frac{VK(C_{peak(steady\ state)})(1 - e^{-Kt})}{(1 - e^{-K\tau})(e^{-Kt'})}$$

$$= \frac{(34.5 \text{ L})(0.015 \text{ hr}^{-1})(29 \text{ mg/L})(1 - e^{-0.015 \text{ hr}^{-1}(48 \text{ hr})})}{(1 - e^{-0.015 \text{ hr}^{-1}(1 \text{ hr})})(e^{-0.015 \text{ hr}^{-1}(2 \text{ hr})})}$$

$$= \frac{7.96 \text{ mg/hr}}{(0.015)(0.970)}$$

$$= 547 \text{ mg, rounded to } 500 \text{ mg}$$

Finally, we must check to see what our trough concentration will be after rounding both dose and dosing interval:

$$C_{trough} = C_{peak} e^{-Kt''} \quad \text{(See } \textbf{Equation 13-5}\text{.)}$$

where:

t'' = time between C_{trough} and C_{peak}

$= \tau - t - t'$

$= 48 - 1 - 2 = 45$ hr

and:

$$C_{trough} = (29 \text{ mg/L}) e^{(-0.015 \text{ hr}^{-1})(45 \text{ hr})}$$

$$= 15.2 \text{ mg/L}$$

CASE 3

A 60-year-old woman, patient BA (weighing 70 kg), is being treated for a hospital-acquired, methicillin-resistant, *Staphylococcus aureus* bacteremia seeding from an infected sacral decubitus ulcer. MIC values for this organism are < 1 mg/L. Her estimated CrCl is 30 mL/minute. Her physician prescribed an initial 1000-mg vancomycin loading dose followed by a maintenance dose of 500 mg (infused over 1 hour) every 12 hours. Per hospital protocol you are required to check all vancomycin dosing and recommend changes as needed.

Problem 3A. Predict the steady-state C_{trough} from this dose, using population average values for K and V. How do they compare to the recommended C_{trough} of > 10 mg/L?

The equation for a one-compartment, intermittent-infusion drug can be used to solve for $C_{peak(steady\ state)}$ and $C_{trough(steady\ state)}$:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = peak plasma concentration at steady state,
K_0 = drug infusion rate (also maintenance dose given over 1 hour),
V = volume of distribution (population estimate for vancomycin of 0.9 L/kg TBW),
K = elimination rate constant (population estimate for vancomycin),
t = infusion time (1 hour in this case),
τ = patient's current dosing interval, and
t' = time between end of infusion and collection of blood sample (2 hours).

First, we must calculate patient BA's K and V values for use in this equation. The estimated K would be:

$$K = 0.00083\ hr^{-1}\ (CrCl) + 0.0044$$

(See **Equation 13-2.**)

$$= 0.00083\ (30) + 0.0044$$
$$= 0.029\ hr^{-1}$$

which we shall round to $0.03\ hr^{-1}$ for ease of calculation.

Patient BA's estimated volume of distribution (V) is calculated from the population estimate of 0.9 L/kg TBW:

$$0.9\ L/kg \times 70\ kg = 63\ L \quad \text{(See Equation 13-1.)}$$

Now that we have these estimates of K and V, we can calculate the C_{peak} and C_{trough} values that would be obtained with this dose of 500 mg every 12 hours. By application of the general equation for a one-compartment, first-order, intermittently infused drug, we get:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = concentration that would result from this dose at steady state,
K_0 = drug infusion rate (maintenance dose per hour),
V = volume of distribution (population estimate for vancomycin),
K = elimination rate constant (population estimate for vancomycin),
t = duration of infusion,
t' = time from end of infusion until concentration is determined (2 hours for peak), and
τ = desired or most appropriate dosing interval.

Therefore:

$$C_{peak(steady\ state)} = \frac{(500\ mg/1\ hr)(1-e^{-0.03\ hr^{-1}(1\ hr)})}{(63\ L)(0.03\ hr^{-1})(1-e^{-0.03\ hr^{-1}(12\ hr)})}e^{-0.03\ hr^{-1}(2\ hr)}$$

$$= \frac{(500\ mg/hr)(0.029)}{(1.89\ L/hr)(0.302)}(0.94)$$

$$= (264.5\ mg/L)(0.096)(0.94)$$

$$= 23.9\ mg/L$$

The peak concentration, in this case, is primarily calculated to continue the math necessary to calculate her trough concentration and can be estimated with the following equation:

$$C_{trough(steady\ state)} = C_{peak(steady\ state)}e^{-Kt}$$

In this case, patient BA's C_{trough} will equal the C_{peak} (drawn 2 hours after the 1-hour infusion) multiplied by the fraction of this C_{peak} remaining after elimination has occurred for t' hours, which, in this case, is 9 hours (12-hour dosing interval minus 3 hours).

The patient's estimated $C_{trough(steady\ state)}$ is calculated as follows:

$$C_{trough(steady\ state)} = (23.9\ mg/L)e^{(-0.03\ hr^{-1})(9\ hr)}$$
$$= (23.9)(0.76)$$
$$= 18.2\ mg/L$$

Now that you know the eventual expected steady-state trough of 18 mg/L, a clinical decision can be made to either decrease dose slightly or wait until patient's vancomycin level is at steady state and obtain a steady-state trough concentration.

Problem 3B. What vancomycin dose would you recommend for patient BA to attain a C_{peak} of 28 mg/L (drawn 2 hours after the end of a 2-hour infusion) and a C_{trough} of 12 mg/L?

Note: You can also change infusion time to 2 hours when recommending a new dose.

Using the estimates of K (0.03 hr^{-1}) and V (63 L), we should first determine the best dosing interval (τ) for patient BA:

$$\tau = \frac{1}{-K}[\ln C_{trough(desired)} - \ln C_{peak(desired)}] + t + t'$$

(See **Equation 13-4.**)

where t is the time of infusion and t' is the time after the end of the infusion. Then:

$$\tau = \frac{1}{-0.03\ hr^{-1}}(\ln 12\ mg/L - \ln 28\ mg/L) + 2\ hr + 2\ hr$$

$$= -33.33\ hr(2.48 - 3.3) + 4\ hr$$

$$= 31.3\ hr, \text{ and we will round down to } 24\ hr$$

$$C_{peak(steady\ state)} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})}e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = desired peak concentration at steady state,

K_0 = drug infusion rate (also maintenance dose you are trying to calculate),

V = volume of distribution (population estimate for vancomycin),

K = elimination rate constant (population estimate for vancomycin),

t = duration of infusion,

t' = time from end of infusion until concentration is determined (2 hours for peak), and

τ = desired or most appropriate dosing interval.

Then:

$$C_{peak(desired)} = \frac{(K_0/2)(1 - e^{-0.03\ hr^{-1}(2\ hr)})}{(63\ L)(0.03\ hr^{-1})(1 - e^{-0.03\ hr^{-1}(24\ hr)})}e^{-0.03\ hr^{-1}(2\ hr)}$$

$$28\ mg/L = \frac{(K_0/2)(0.058)}{(1.89)(0.66)}(0.94)$$

$$= (K_0/2)(0.046)(0.94)$$

$$28 = (K_0/2)(0.044)$$

$$28 / 0.044 = (K_0/2)$$

$$636 = (K_0/2)$$

$$K_0 = 1272\ mg \text{ rounded down to } 1200\ mg$$

Note: Answer of 636 mg/hr for two infusions = 1272 because we rounded our interval to every 24 hours.

The expected trough concentration can now be calculated:

$$C_{trough(steady\ state)} = C_{peak(steady\ state)}e^{-Kt}$$

(See **Equation 13-5.**)

In this case, C_{trough} will equal the C_{peak} (drawn 2 hours after the 2-hour infusion is complete) multiplied by the fraction of this C_{peak} remaining after elimination has occurred for t hours, which, in this case, is 20 hours (24-hour dosing interval minus 2 hours minus 2 hours). So:

$$C_{trough(steady\ state)} = (28\ mg/L)e^{(-0.03\ hr^{-1})(20\ hr)}$$

$$= 28\ (0.55)$$

$$= 15.4\ mg/L$$

Thus, a dose of 1300 mg every 24 hours will yield an estimated C_{peak} of 28 mg/L and an estimated C_{trough} of 15.4 mg/L, which should be adequate in BA's case.

Clinical Correlate

Don't let these equations intimidate you. Try to develop a step-by-step model to walk you through the calculations, such as:

- Determine patient-specific K and V values. If these values are not known, use population estimates.
- Determine the dosing interval.
- Determine the drug infusion rate (K_0).
- Check the trough to make sure it is within your desired range.

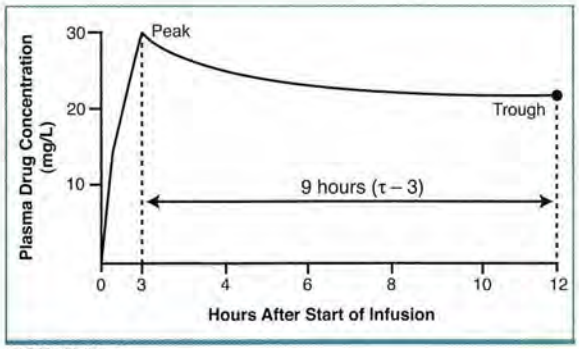

FIGURE 13-6.
Time between peak and trough

Problem 3C. Despite your dosing recommendation, BA continued to receive her original dose of 500 mg every 12 hours (infused over 1 hour) with resultant steady-state peak and trough levels of 30 and 22 mg/L, respectively (**Figure 13-6**). Adjust patient BA's dose, this time using her specific pharmacokinetic parameters, to give a C_{peak} of approximately 28 mg/L and a $C_{trough(steady\ state)}$ of approximately 12 mg/L.

To adjust this patient's dose, we must first determine her real K and V values, then calculate a new dosing interval, and finally solve for a new maintenance dose.

To calculate K, we can use:

$$K = -\frac{\ln C_{trough} - \ln C_{peak}}{\tau - t - t'}$$

$$= -\frac{\ln 22\ mg/L - \ln 30\ mg/L}{9\ hr}$$

$$= \frac{3.09 - 3.40}{9\ hr}$$

$$= \frac{0.31}{9\ hr}$$

$$= 0.034\ hr^{-1}$$

(See **Equation 3-1.**)

To calculate V, we can use:

$$C_{peak(steady\ state)} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = measured steady state peak plasma concentration (30 mg/L) drawn 2 hours after end of a 1-hour infusion,

K_0 = drug infusion rate (maintenance dose of 500 mg, infused over 1 hour),

V = volume of distribution (unknown),

K = elimination rate constant calculated from C_{peak} and C_{trough} (0.034 hr^{-1}),

t = infusion time (1 hour),

t' = time from end of infusion until concentration is determined (2 hours for peak) (see Figure 13.6), and

τ = dosing interval at time concentrations are obtained (12 hours).

By substituting the above values, we obtain:

$$30\ mg/L = \frac{(500\ mg/1\ hr)(1 - e^{-0.034\ hr^{-1}(1\ hr)})}{V(0.034\ hr^{-1})(1 - e^{-0.034\ hr^{-1}(12\ hr)})} e^{-0.034\ hr^{-1}(2\ hr)}$$

$$= \frac{(500\ mg/hr)(0.033)}{V(0.034\ hr^{-1})(0.34)}(0.93)$$

$$V = 42.6\ L$$

Note the differences between the previously estimated K and V of 0.03 hr^{-1} and 63 L and the calculated values of 0.034 hr^{-1} and 42.6 L. The K values are quite similar; however, the V is much smaller than originally calculated.

Now, to calculate the best dosing interval, once again infused over only 1 hour in this case, to get a C_{peak} of 28 mg/L and a $C_{trough(steady\ state)}$ of approximately 12 mg/L, we would use:

$$\tau = \frac{1}{-K}[\ln C_{trough(desired)} - \ln C_{peak(desired)}] + t + t'$$

$$= \frac{1}{-0.034\ hr^{-1}}[\ln 12\ mg/L - \ln 28\ mg/L] + 1\ hr + 2\ hr$$

$$= \frac{1}{-0.034\ hr^{-1}}[2.48 - 3.33] + 3\ hr$$

$$= 25\ hr, \text{ rounded to } 24\ hr$$

(See **Equation 13-4.**)

The new maintenance dose now can be calculated:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = desired peak concentration at steady state (28 mg/L),

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour),

V = volume of distribution (42.6 L),

K = elimination rate constant calculated from C_{peak} and C_{trough} (0.034 hr^{-1}),

t = infusion time (1 hour),

t' = time from end of infusion until concentration is determined (2 hours for peak), and

τ = desired or most appropriate dosing interval (24 hours).

Then:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-0.034\ hr^{-1}(1\ hr)})}{(42.6\ L)(0.034\ hr^{-1})(1-e^{-0.034\ hr^{-1}(24\ hr)})}e^{-0.034\ hr^{-1}(2\ hr)}$$

$$28\ mg/L = \frac{K_0(0.033)}{(1.45)(0.56)}(0.93)$$

$$= \frac{K_0(0.031)}{0.81}$$

$$K_0 = 740\ mg$$

Being conservative, we would round this dose to 750 mg, which would only slightly raise the actual peak value from 28 to approximately 28.4 mg/L. This calculation is shown below:

$$(750\ mg/740\ mg) \times 28\ mg/L = 28.4\ mg/L$$

Problem 3D. Calculate the $C_{trough(steady\ state)}$ for patient BA if she receives the new dose of 750 mg every 24 hours.

We can use the following equation, where t'' is now the number of hours between the peak and trough ($t'' = \tau - t - t'$). Therefore, $t'' = 21$ hours.

$$C_{trough(steady\ state)} = C_{peak(steady\ state)}e^{-t''}$$

(See **Equation 13-5.**)

$$= (28.4\ mg/L)e^{(-0.034\ hr^{-1})(21\ hr)}$$

$$= 13.9\ mg/L$$

This new dose of 750 mg every 24 hours based on patient-specific PK parameters will then give a C_{peak} of approximately 28 mg/L and a C_{trough} of approximately 14 mg/L.

Problem 3E. Because patient BA's C_{trough} of 22 mg/L is too high from the regimen of 500 mg every 12 hours, the dose will need to be held for a certain amount of time before beginning the new dose of 750 mg every 24 hours.

Before changing to 750 mg every 24 hours, you must wait for patient BA's C_{trough} of 22 mg/L to decrease to the desired C_{trough} of approximately 12 mg/L. The formula for calculating the number of hours to hold the dose is:

$$C_{trough(desired)} = C_{trough(actual)}e^{-Kt}$$ (See **Equation 3-2.**)

where t is the amount of time to hold the dose. This formula is an application of the general formula (see Lesson 3) that the concentration at any time equals a previous concentration multiplied by the fraction remaining:

$$C = C_0e^{-Kt}$$

where:

C = drug concentration at time t,

C_0 = drug concentration at some earlier time or time zero, and

e^{-Kt} = fraction of original or previous concentration remaining.

In patient BA's case:

$$12\ mg/L = (22\ mg/L)e^{(-0.034\ hr^{-1})(t)}$$

$$0.55\ mg/L = e^{(-0.034\ hr^{-1})(t)}$$

Next, take the natural logarithm of both sides:

$$\ln 0.55 = \ln\ (e^{(-0.034\ hr^{-1})(t)})$$

$$-0.61 = -0.034(t)$$

$$t = 17.9\ hr$$

We should hold this patient's dose for an additional 18 hours after the next C_{trough} and then begin her new dose. The same equation can be used to determine the amount of time to hold the dose from the last C_{peak} of 30 mg/L. Again, the general equation is:

$$C = C_0 e^{-Kt} \quad \text{(See Equation 3-2.)}$$

where:

- C = drug concentration at time t (representing here the desired C_{trough} of 12 mg/L),
- C_0 = drug concentration at some earlier time (representing here C_{peak} of 30 mg/L), and
- e^{-Kt} = fraction of previous concentration remaining.

In patient BA's case:

$$12 \text{ mg/L} = (30 \text{ mg/L}) e^{(-0.034 \text{ hr}^{-1})(t)}$$

$$0.40 \text{ mg/L} = e^{(-0.034 \text{ hr}^{-1})(t)}$$

Next, take the natural logarithm of both sides:

$$\ln 0.40 = \ln (e^{(-0.034 \text{ hr}^{-1})(t)})$$

$$-0.92 = -0.034(t)$$

$$27 \text{ hr} = t$$

We should hold this patient's dose for an additional 27 hours after the C_{peak} and then begin her new dose. Note that you can calculate time to hold using either C_{peak} or C_{trough}; both methods give the correct answer, but you **must** examine where you are in the dosing versus serum concentration sequence.

A more intuitive method for estimating the time to hold patient BA's dose is by examination of the vancomycin half-life. We know that the drug concentration decreases by half over each half-life. We can estimate how many drug half-lives to wait for her concentration to approach our desired amount of 12 mg/L as follows. For patient BA (C_{trough} of 22 mg/L and $T½$ of 20.3 hours [0.693/0.034]), the concentration will drop by one-half from 22 to 11 mg/L in one half-life of 20 hours. Because a concentration of 11 mg/L is acceptable, we need to hold only the **next scheduled dose** for an additional 20 hours before beginning the new dose of 750 mg every 24 hours.

CASE 4

A 65-year-old man, patient RK, has a history of subacute bacterial endocarditis secondary to a mitral valve replacement 5 years ago. He is currently hospitalized for methicillin-resistant *Staphylococcus aureus* bacteremia. He has been treated with 750 mg of vancomycin every 16 hours for the last 10 days. His most recent C_{peak} was 26 mg/L (drawn 2 hours after a 2-hour vancomycin infusion), and his most recent C_{trough} was 9 mg/L.

Problem 4. Patient RK's physician wants to discharge him and allow a local home infusion company to administer his vancomycin on a once-a-day basis. You are asked to determine if it is possible to obtain a C_{trough} of > 10 mg/L with a once-a-day dose. What is your response?

Before answering this question, we must be sure we know what the question is asking. Basically, this question is asking whether, based on the patient's pharmacokinetic parameters, a dose can be given to obtain a satisfactory C_{peak} and C_{trough} given a dosing interval of 24 hours.

First, we must determine patient RK's pharmacokinetic parameters based on his C_{peak} of 26 mg/L and C_{trough} of 9 mg/L. To calculate K, we can use:

$$-K = \frac{\ln C_{trough(measured)} - \ln C_{peak(measured)}}{\tau - t - t'}$$

(See **Equation 3-1.**)

where t' represents 2 hours, the number of hours after the infusion that the C_{peak} was drawn. Then:

$$K = -\frac{\ln 9 \text{ mg/L} - \ln 26 \text{ mg/L}}{12 \text{ hr}}$$

$$= -\frac{2.20 - 3.26}{12 \text{ hr}}$$

$$= 0.088 \text{ hr}^{-1}$$

To calculate V, we can use:

$$C_{peak(steady\ state)} = \frac{K_0(1 - e^{-Kt'})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See **Equation 13-3.**)

where:

$C_{peak(steady\ state)}$ = measured peak plasma concentration (26 mg/L),

K_0 = drug infusion rate (also maintenance dose of 750 mg),

V = volume of distribution (unknown),

K = elimination rate constant calculated from C_{peak} and C_{trough} (0.088 hr^{-1}),

t = duration of infusion (2 hours),

t' = time from end of infusion until concentration is determined (2 hours for peak), and

τ = dosing interval at time concentrations are obtained (16 hours).

By substituting the above values, we obtain:

$$26\ mg/L = \frac{(750\ mg/2)(1-e^{-0.088\ hr^{-1}(2\ hr)})}{V(0.088\ hr^{-1})(1-e^{-0.088\ hr^{-1}(16\ hr)})} e^{-0.088\ hr^{-1}(2\ hr)}$$

$$= \frac{(750\ mg/2)(0.16)}{V(0.088\ hr^{-1})(0.755)}(0.93)$$

$$V = 32.3\ L$$

Next, we use our general equation to solve for K_0 (maintenance dose) with our predetermined 24-hour dosing interval:

$$C_{peak(steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})} e^{-Kt'}$$

where:

$C_{peak(steady\ state)}$ = desired peak concentration at steady state (26 mg/L),

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour infused for 2 hours),

V = calculated volume of distribution (32.3 L),

K = elimination rate constant calculated from C_{peak} and C_{trough} (0.088 hr^{-1}),

t = duration of infusion time (2 hours),

t' = time from end of infusion until concentration is determined (2 hours for peak), and

τ = dosing interval desired (24 hours).

By substituting the above values, we obtain:

$$26\ mg/L = \frac{(K_0/2)(1-e^{-0.088\ hr^{-1}(2\ hr)})}{(32.3\ L)(0.088\ hr^{-1})(1-e^{-0.088\ hr^{-1}(24\ hr)})} e^{-0.088\ hr^{-1}(2\ hr)}$$

$$26\ mg/L = \frac{(K_0/2)(0.16)}{(2.84)(0.88)}(0.84)$$

$$K_0/2 = 483\ mg$$

$$K_0 = 966\ mg,\ round\ to\ 1000\ mg,\ infused\ over\ 2\ hours$$

Finally, we must check to see that our C_{trough} concentration with this dose is acceptable.

$$C_{trough(steady\ state)} = C_{peak(steady\ state)} e^{-Kt''}$$

(See **Equation 13-5.**)

In this case, patient RK's C_{trough} will be equal to his C_{peak} of 26 mg/L multiplied by the fraction of the C_{peak} remaining after elimination has occurred for t'' hours, which, in this case, is 20 hours (24-hour dosing interval minus t [2 hours] minus t' [2 hours]).

Therefore:

$$C_{trough(steady\ state)} = (26\ mg/L)e^{(-0.088\ hr^{-1})(20\ hr)}$$

$$= 4.2\ mg/L$$

We can conclude that 1000 mg every 24 hours will not yield a trough concentration > 10 mg/L. In fact, the dose would need to be doubled to 2000 mg every 24 hours to accomplish this, which would, in turn, double the expected peak concentration from 26 mg/L to 52 mg/L.

Trough-Only Vancomycin Pharmacokinetics

Because the trough vancomycin concentration has been shown to be most associated with drug efficacy and decreased development of microorganism resistance and yet also associated with nephrotoxicity, many practitioners simply use a ratio and proportion method of dosing adjustment based solely on the trough level. For instance, if trough = 8 on a dose of 750 mg every 12 hours, they simply double both values and give 1500 mg every 12 hours, to yield a trough of approximately twice the previous value (from 8 to 16 mg/L). Unfortunately,

single-trough-level-only dosing methods do not allow for calculation of individual patient–specific values for vancomycin clearance (CL_{vanco}), volume of distribution (V), elimination rate constant (K), or estimated C_{peakss}, and therefore, makes a concomitant change in dosing interval somewhat of a guessing game. Consequently, several methods have been devised that attempt to estimate one vancomycin population estimate such as K or Vd and solve for the other estimate to obtain a "better" C_{peakss}. Although there are many iterations of this method, these single-trough methods estimate either K or Vd and then solve for the other. For instance, some practitioners use the Matzke equation (as shown in **Equation 13-3**) to estimate K and solve for V or vice versa. Another popular and intuitive method is the Ambrose-Winter method that uses the simple equation of

$$C_{peakss} = (dose/V) + C_{troughss}$$

This equation allows you to estimate a peak concentration based on the simple relationship that Concentration = amount of drug (or dose)/Volume and then using this value of C_{peakss} (but now written as $[dose/V] + C_{troughss}$) where $(dose/V) + C_{troughss}$ is simply a re-expression of C_{peakss} as also shown above.

Although these methods are not as accurate as having both a "real" peak and trough serum concentration, they are more accurate than using estimates for both K and Vd and may be adequate in most clinical situations.

References

1. Rybak MJ, Lomaestro BM, Rotscahfer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis.* 2009;49(3):325–327.
2. Ambrose PJ, Winter ME. Vancomycin. In: Winter ME. *Basic Clinical Pharmacokinetics.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:451–476.

Discussion Points

D1. In Case 1, Problem 1A, suppose BW is actually 6' 2" tall, weighs 106 kg, and has an estimated creatinine clearance of 61 mL/minute. How would your maintenance dose differ to achieve plasma concentrations of 22 mg/L for the peak (2 hours after a 2-hour infusion) and approximately 12 mg/L for the trough?

D2. Steady-state serum concentrations resulting from the maintenance dose you calculated in D-1 were reported by the laboratory as: peak, 17.8 mg/L and trough, 10.2 mg/L. Calculate a new maintenance dose to give our desired peak and trough concentrations of 22 mg/L and approximately 12 mg/L, respectively.

D3. Assume that BA in Case 3 actually received a vancomycin 1200-mg loading dose followed by a maintenance dose of 1000 mg (over 2 hours) every 12 hours. Predict the steady-state peak and trough levels that would result from this maintenance dose, using population average values for *K* and *V*.

D4. Assume that the first dose for a patient (a 41-year-old female, 5' 6", 148 lbs, with positive blood cultures for methicillin-resistant *Staphylococcus aureus*; serum creatinine, 1.2 mg/dL; white blood cell count, 18,300/mm^3, 10% bands; receiving 1000 mg of vancomycin IV every 12 hours) is scheduled for 8 AM on 12/1. Describe in detail the process of how you determine when serum levels (and what type of levels) should be obtained. Then write an order as it would appear in the Physician's Order section of the patient's medical record for how serum levels should be obtained. This order should be grammatically correct, include only approved abbreviations, and provide sufficient detail that nursing services can easily follow your instructions without having to contact you for further clarification.

D5. Based on your experience in the provision of direct patient care, design a pharmacy-managed vancomycin dosing protocol that could be used in your practice setting. This protocol should be written from the standpoint that the pharmacist is providing complete dosing and monitoring of vancomycin in a patient case (instead of simply providing recommendations to a physician to manage). All steps required to effectively dose and monitor (including equations used) a patient for whom vancomycin is prescribed should be included. Describe in detail how you would monitor this drug using serum concentrations. Write the order for this drug as it would appear in the Physician's Order section of the patient's medical record.

LESSON 14
Theophylline

Methylxanthines, including theophylline and aminophylline, have been used in the management of asthma and chronic obstructive pulmonary disease (COPD) for more than five decades. With time, the use of these agents has declined as a result of the advent of alternative therapy, including beta-2 agonists, anticholinergics, corticosteroids, mast cell stabilizers, leukotriene modifiers, and immunomodulators. Although methylxanthines produce little therapeutic benefits for the patient with asthma,[1] these agents may reduce dyspnea, increase exercise tolerance, and improve respiratory drive in patients with COPD.[2] At the same time, theophylline is an excellent agent for illustrating pharmacokinetic concepts associated with the continuous intravenous infusion model. Cases in this lesson focus on patient-specific dosing of aminophylline and theophylline.

Theophylline typically follows first-order pharmacokinetics in most patients with serum concentrations within the therapeutic range of 5–15 mg/L. It may undergo nonlinear, or Michaelis–Menten, pharmacokinetics (see Lesson 10) when serum concentrations are within this range; however, this is more likely to occur at concentrations exceeding 15 mg/L.[3]

Theophylline is eliminated from circulation through hepatic oxidative metabolism (cytochrome P450) and has a low intrinsic clearance (see Lesson 9). Therefore, total hepatic clearance of theophylline is determined by the intrinsic clearance of the liver and is not dependent on liver blood flow. Disease states, drugs, and other factors that may influence theophylline clearance are found in **Table 14-1**.

Theophylline is usually administered intravenously or orally. When theophylline derivatives are used, the theophylline dose equivalent should be calculated. For example, aminophylline is 80% theophylline. Therefore, to obtain the theophylline dose equivalent, the aminophylline dose should be multiplied by 0.8.

Many different oral formulations of theophylline are available. Some of these are rapidly absorbed after administration. Others are designed to slowly release drug in the gastrointestinal tract for up to 24 hours. The type of oral product used directly affects pharmacokinetic calculations.

TABLE 14-1. Factors and Drugs That Alter Theophylline Clearance

Factors	Total Body Clearance (L/kg/hour)	Clearance Adjustment (× 0.04 L/kg/hour)
Hepatic disease	0.02	0.5
Acute pulmonary edema	0.02	0.5
Severe chronic obstructive pulmonary disease	0.03	0.8
Heart failure	0.016	0.5
Cor pulmonale	0.028	0.7
Cigarette smoking	0.063	1.6
Former cigarette smoking (quit > 2 years)	0.051	1.2
Marijuana smoking	0.072	1.7
Marijuana and cigarettes	0.09	2.2
Elderly cigarette smokers	0.045	1.1

Drugs	Clearance Adjustment (× 0.04 L/kg/hour)
Cimetidine (after 2 or more days)	0.5–0.7
Oral contraceptives	0.7
Interferon	0.15
Ciprofloxacin	0.7–0.75
Diltiazem	0.8–0.9
Norfloxacin	0.85
Phenytoin	1.35–1.5
Phenobarbital	1.35–1.5
Erythromycin	0.75–0.8
Propranolol	0.5–0.7
Verapamil	0.8–0.9
Rifampin	1.35–1.5
Phenytoin + smoking	1.9

CASE 1

MA is a 62-year-old, 73-kg, man with a 30-year history of mild COPD that has been satisfactorily controlled with beta-2 agonist, ipratropium, and inhaled steroid therapy. However, over the past two months, MA has experienced increased difficulty in breathing. His physician wishes to admit him to the hospital and initiate intravenous aminophylline.

Problem 1A. Calculate an appropriate loading dose of aminophylline for MA that will result in a theophylline concentration of 14 mcg/mL.

To calculate a loading dose of aminophylline requires that we know the desired theophylline plasma concentration, the patient's theophylline volume of distribution, the aminophylline salt equivalent for theophylline, and the fraction of drug administered that reaches the systemic circulation.

In this case, the desired plasma theophylline concentration is 14 mcg/mL, the aminophylline salt equivalent (S) is 0.8, and the fraction of drug administered reaching the systemic circulation (F) is 1.

The one remaining factor that is necessary to make this loading dose calculation is the patient's theophylline volume of distribution (V). This is calculated from the patient's weight and the expected volume (in liters per kilogram) from published literature:

14-1 $$V\,(\text{L}) = \text{weight (kg)} \times 0.5\ \text{L/kg}$$
$$= 73\ \text{kg}\ (0.5\ \text{L/kg})$$
$$= 36.5\ \text{L}$$

Clinical Correlate

For theophylline, the patient's actual body weight should be used to calculate the volume of distribution unless the patient's actual weight is more than 50% above his or her ideal body weight. In patients more than 50% above ideal body weight, volume of distribution should be calculated using ideal body weight.

Based on the information we now have, we can calculate an aminophylline loading dose for MA.

The basic loading dose equation can be derived from the plasma concentration equation we learned in Lesson 1.

$$\text{concentration} = \frac{\text{amount of drug in body}}{\text{volume in which drug is distributed}}$$

$$C = \frac{X}{V}$$

(See **Equation 1-1**.)

We can rewrite this equation to:

$$D = C \times V$$

Taking into consideration the S and F values for aminophylline, we can rewrite the above variation of **Equation 1-1** as follows:

14-2 $$D = \frac{\text{Cpd}V}{SF}$$

where:

D = the loading dose (milligrams),
Cpd = the desired concentration (milligrams per liter),
V = the volume of distribution (liters),
S = salt form, and
F = bioavailability, which is equal to 1 for drugs given intravenously.

Substituting known values for these parameters,

$$D = \frac{14\ \text{mg/L} \times (36.5\ \text{L})}{0.8}$$
$$= 638.75\ \text{mg}$$
$$= 640\ \text{mg}$$

This 640-mg aminophylline loading dose will produce a serum concentration slightly greater than 14 mcg/mL.

Note: Remember, aminophylline is a salt form of theophylline and contains approximately 80% theophylline equivalents.

Problem 1B. The loading dose is to be administered over a 30-minute interval. An aminophylline maintenance infusion is to be started immediately on completion of the loading dose. Suggest an aminophylline infusion rate for MA that will achieve a plasma theophylline concentration of 12 mcg/mL.

STEP A

The first step in solving this problem is to estimate MA's theophylline clearance. This can be accomplished by using the following equation:

14-3 $$\text{Cl} = (0.04\ \text{L/kg/hr}) \times \text{weight (kg)}$$

where:

Cl = clearance (L/hour; clearance is based on the patient's actual body weight), and
0.04 L/kg/hour = population estimate found in the literature.

Therefore,

$$\text{Cl} = (0.04\ \text{L/kg/hr}) \times \text{weight (kg)}$$
$$= (0.04\ \text{L/kg/hr}) \times 73\ \text{kg}$$
$$= 2.92\ \text{L/hr}$$

STEP B

To solve for a maintenance dose (milligrams per hour), we can rearrange and slightly modify **Equation 4-3** to **Equation 14-4** as follows:

$$\bar{C} = \frac{\text{dose}}{Cl_t \times \tau}$$

(See **Equation 4-3.**)

14-4

$$D = \frac{\bar{C}\, p_{ss}\ Cl\tau}{SF}$$

where:

- D = the maintenance dose (milligrams per hour),
- $\bar{C}\, p_{ss}$ = average steady-state concentration desired (micrograms per milliliter),
- Cl = clearance (liters per hour),
- S = salt form,
- F = bioavailability, and
- τ = dosing interval, which is 1 hour for a continuous intravenous infusion.

After inserting the Cl value calculated in Step A, S and F values, a dosing interval of one hour, and our desired serum concentration for $\bar{C}$, we can solve for the maintenance dose:

$$D = \frac{12 \text{ mcg/mL} \times 2.92 \text{ L/hr} \times 1 \text{ hr}}{0.8}$$

$$= 43.8 \text{ mg/hr}$$

$$= 44 \text{ mg/hr}$$

Figure 14-1 demonstrates the relationship between serum levels achieved with the loading and maintenance doses of theophylline or aminophylline.

Problem 1C. How long will it take for MA's theophylline therapy to reach steady state?

- Steady state is reached once a given dose of a drug is administered for 5 half-lives of the drug.
- Half-life is determined by the equation $T½ = 0.693/K$.

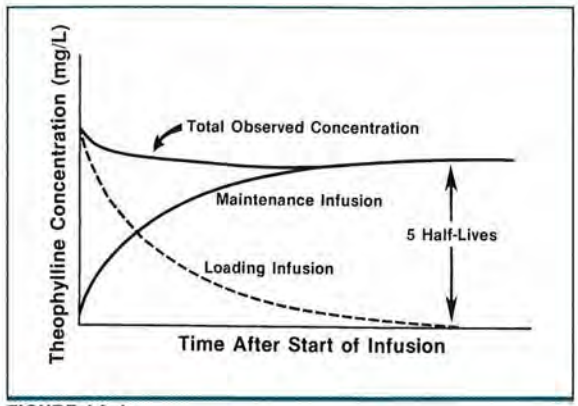

FIGURE 14-1.
Plasma concentrations with a loading dose and continuous infusion of theophylline or aminophylline.

- This requires that we know the value for K in this patient.

Using the equation Cl = K x V, we can use our estimated values for Cl and V to estimate K.

$$Cl = K \times V$$

$$2.92 \text{ L/hr} = K \times (0.5 \text{ L/kg} \times 73 \text{ kg})$$

$$= K \times 36.5 \text{ L}$$

$$K = 0.08 \text{ hr}^{-1}$$

Now, substituting K into our half-life equation, we can solve for half-life.

$$T½ = 0.693/K$$

$$= 0.693/0.08$$

$$= 8.7 \text{ hours}$$

Steady state will be reached in 5 half-lives.

$$5 \times 8.7 \text{ hours} = 43.5 \text{ hours}$$

Problem 1D. MA's steady-state theophylline serum concentration is 11.6 mcg/mL. Is there any reason to change his dose at this time?

As long as MA is improving clinically and not experiencing theophylline adverse effects, it would be appropriate to leave his dose as is.

CASE 2

CJ is a 48-year-old, 60-kg, woman who is admitted to the hospital for treatment of severe chronic bronchitis. She has a history of cigarette smoking since age 14 and is currently receiving verapamil for high blood pressure.

Problem 2A. Estimate CJ's volume of distribution and clearance for theophylline.

To estimate CJ's volume of distribution (see **Equation 14-1**):

$$V(\text{L}) = \text{weight (kg)} \times 0.5\ \text{L/kg}$$

$$= 60\ \text{kg}\ (0.5\ \text{L/kg})$$

$$= 30\ \text{L}$$

To estimate CJ's clearance (see **Equation 14-3**):

$$\text{Cl} = (0.04\ \text{L/kg/hr}) \times \text{weight (kg)} \times (\text{adjustment factors})$$

$$= (0.04\ \text{L/kg/hr}) \times 60\ \text{kg} \times (0.8) \times (1.6) \times (0.8)$$

$$= 2.46\ \text{L/hr}$$

(The clearance adjustment factors of 0.8, 1.6, and 0.8 are found in **Table 14-1** for severe bronchitis [severe COPD], cigarette smoking and verapamil, respectively.)

Problem 2B. Calculate an aminophylline loading dose for CJ that will achieve an initial plasma concentration of 12 mcg/mL. The dose will be given as an infusion over 30 minutes.

To calculate the loading dose:

$$D = \frac{C_{pd} V}{SF}$$

(See **Equation 14-2.**)

$$D = \frac{12\ \text{mcg/mL} \times 30\ \text{L}}{0.8}$$

$$= 450\ \text{mg}$$

Problem 2C. Calculate an infusion rate of aminophylline that will maintain CJ's serum concentration at 12 mcg/mL.

To determine the infusion rate:

$$D = \frac{\bar{C}_{p_{ss}}\ \text{Cl}\tau}{SF}$$

(See **Equation 14-4.**)

$$D = \frac{12\ \text{mcg/mL} \times 2.46\ \text{L/hr} \times 1\ \text{hr}}{0.8}$$

$$= 36.9\ \text{mg/hr}$$

$$= 37\ \text{mg/hr}$$

Problem 2D. A steady-state theophylline serum concentration is reported by the lab as 18.2 mcg/mL. Calculate a new aminophylline maintenance dose to achieve a steady-state theophylline serum concentration of 12 mcg/mL.

STEP A

The first step in calculating a new aminophylline maintenance dose for CJ is to solve for her actual theophylline clearance. When calculating her initial maintenance dose, we estimated clearance using a population value. Now that we have a measured steady-state serum concentration, we can calculate an actual value.

To determine CJ's actual theophylline clearance, we can rearrange **Equation 14-4** in Problem 1B and calculate this parameter as follows:

$$D = \frac{\bar{C}_{p_{ss}}\ \text{Cl}\tau}{SF}$$

Rearrange to solve for Cl:

$$\text{Cl} = \frac{DSF}{\bar{C}_{p_{ss}}\tau}$$

(See **Equation 14-4.**)

where:

Cl = clearance (liters per hour),

D = maintenance dose (milligrams per hour),

S = salt form,
F = bioavailability, and
$\bar{C}\,p_{ss}$ = average steady-state concentration (micrograms per milliliter).

$$Cl = \frac{37\ mg/hr \times 0.8 \times 1}{18.2\ mcg/mL}$$

$$= 1.63\ L/hr$$

Notice that we estimated CJ's theophylline Cl as 2.46 L/hour, but her actual value is 1.63 L/hr.

STEP B

Now that we have CJ's actual theophylline clearance, we can calculate a new maintenance dose that will give us the desired theophylline serum concentration of 12 mcg/mL:

$$D = \frac{\bar{C}\,p_{ss}\ Cl\tau}{SF}$$

(See **Equation 14-4.**)

$$D = \frac{12\ mcg/mL \times 1.63\ L/hr \times 1\ hr}{0.8 \times 1}$$

$$= 24.45\ mg/hr$$

$$= 25\ mg/hr$$

STEP C

Before we can begin this new maintenance dose of aminophylline in CJ, it is necessary to determine how long we must hold her current dose until her serum theophylline concentration declines to an acceptable value. We will choose a level of 12 mcg/mL. To determine how long it will be necessary to wait before starting this new maintenance dose, we need to determine CJ's theophylline elimination rate. We will make the calculation using her actual clearance value. Using the following formula:

$$K = \frac{Cl}{V}$$

(See **Equation 3-4.**)

where:

K = elimination rate constant (hr^{-1}),
Cl = clearance (liters per hour), and
V = volume of distribution (liters).

$$K = 1.63\ L/hr/30\ L$$

$$= 0.054\ hr^{-1}$$

Next we can determine the time we need to wait by using the following equation:

$$C = C_0 e^{-Kt}$$ (See **Equation 3-2.**)

where:

t = time to wait (hours),
C = desired concentration (micrograms per milliliter),
C_0 = current concentration (micrograms per milliliter), and
K = elimination rate constant (hr^{-1}).

Therefore:

$$12 = 18.2e^{-0.054t}$$

$$12/18.2 = e^{-0.054t}$$

$$0.659 = e^{-0.054t}$$

$$\ln 0.659 = \ln e^{-0.054t}$$

$$-0.417 = -0.054t$$

$$t = 7.7\ hours$$

CJ would receive the new infusion of 25 mg/hour starting 8 hours after discontinuing the previous infusion of 37 mg/hour.

Clinical Correlate

The most significant side effects from theophylline occur at serum concentrations higher than 20 mcg/mL. These include nausea, vomiting, headache, diarrhea, irritability, and insomnia. At concentrations higher than 35 mcg/mL, major adverse effects include hyperglycemia, hypotension, cardiac arrhythmias, seizures, brain damage, and death.

CASE 3

SR is a 52-kg patient admitted to the emergency department with difficulty breathing. He has been prescribed theophylline on an outpatient basis but admits his compliance to his medication regimen is poor. A STAT theophylline level is reported as 3.9 mcg/mL.

Problem 3A. Calculate an appropriate theophylline loading dose to give SR a serum level of 14 mcg/mL.

STEP A

Estimate SR's theophylline volume of distribution.

$$V = \text{weight (kg)} \times 0.5 \text{ L/kg}$$
$$= 52 \text{ kg} \times 0.5 \text{ L/kg}$$
$$= 26 \text{ L}$$

STEP B

Using SR's estimated V, calculate an appropriate theophylline loading dose.

In this situation, we will slightly modify the loading dose **Equation 14-2** to the following:

$$D = \frac{(Cpd\text{-}Cpi)V}{SF}$$

(See **Equation 14-2**.)

where:

- D = the loading dose,
- Cpd = the desired concentration (milligrams per liter),
- Cpi = the initial concentration (milligrams per liter),
- V = the volume of distribution (liters),
- S = salt form, and
- F = bioavailability, which is equal to 1 for drugs administered intravenously.

$$D = \frac{(14 \text{ mcg/mL} - 3.9 \text{ mcg/mL}) \times 26 \text{ L}}{1 \times 1}$$
$$= 262.6 \text{ mg}$$
$$= 260 \text{ mg}$$

This 260-mg theophylline loading dose will result in a serum concentration slightly less than 14 mg/L.

Notice in this situation we are using a value of 1 for S (theophylline is not in a salt form).

Problem 3B. Calculate a theophylline maintenance dose that will maintain SR's serum concentration at 12 mcg/mL.

STEP A

As we saw in Case 1, the first step in solving this problem is to estimate SR's theophylline clearance. This can be accomplished by using the following equation:

14-3 $$Cl = (0.04 \text{ L/kg/hr}) \times \text{weight (kg)}$$

where:

- Cl = clearance (L/hour; clearance is based on the patient's actual body weight), and
- 0.04 L/kg/hour = population estimate found in the literature.

Therefore,

$$Cl = (0.04 \text{ L/kg/hr}) \times \text{weight (kg)}$$
$$= (0.04 \text{ L/kg/hr}) \times 52 \text{ kg}$$
$$= 2.08 \text{ L/hr}$$

STEP B

To solve for a maintenance dose (milligrams per hour), we can rearrange and slightly modify **Equation 4-3** to **Equation 14-4** as follows:

$$\bar{C} = \frac{\text{dose}}{Cl_t \times \tau}$$

(See **Equation 4-3**.)

14-4 $$D = \frac{\bar{C}\, p_{ss}\, Cl\tau}{SF}$$

where:

D = the maintenance dose (milligrams per hour),

$\bar{C}p_{ss}$ = average steady-state concentration desired (micrograms per milliliter),

Cl = clearance (liters per hour),

S = salt form,

F = bioavailability, and

t = dosing interval, which is 1 hour for a continuous intravenous infusion.

After inserting the Cl value calculated in Step A, S and F values, a dosing interval of one hour, and our desired serum concentration for $\bar{C}p_{ss}$, we can solve for the maintenance dose:

$$D = \frac{12 \text{ mcg/mL} \times 2.08 \text{ L/hr} \times 1 \text{ hr}}{1 \times 1}$$

$$= 24.96 \text{ mg/hr}$$

$$= 25 \text{ mg/hr}$$

Notice that both S and F for theophylline are 1.

Problem 3C. SR has been stabilized on his 25 mg/hr of theophylline regimen, and his steady-state serum theophylline level is now 13.2 mcg/mL. Calculate a dose of sustained-release theophylline for SR to maintain a theophylline serum concentration of 12 mcg/mL.

Many theophylline sustained-release formulations follow the same pharmacokinetic profile as continuous intravenous infusions. Therefore, we can easily make a conversion from a continuous infusion to an oral sustained-release formulation as follows:

STEP A

Calculate SR's theophylline clearance.

$$Cl = \frac{DSF}{\bar{C}p_{ss}\tau}$$

(See **Equation 14-4**.)

$$Cl = \frac{25 \text{ mg/hr} \times 1 \times 1}{13.2 \text{ mcg/mL} \times 1}$$

$$= 1.89 \text{ L/hr}$$

STEP B

Calculate the dose to be given orally every 12 hours.

$$D = \frac{\bar{C}p_{ss}\, Cl\tau}{SF}$$

(See **Equation 14-3**.)

where:

D = the maintenance dose (milligrams),

$\bar{C}p_{ss}$ = the desired average steady-state concentration (micrograms per milliliter),

Cl = clearance (liters per hour),

τ = dosing interval (hours),

S = salt form

F = bioavailability

$$D = \frac{12 \text{ mcg/mL} \times 2.08 \text{ L/hr} \times 12 \text{ hr}}{1 \times 1}$$

$$= 299.5 \text{ mg}$$

$$= 300 \text{ mg}$$

SR should receive 300 mg of sustained-release theophylline orally every 12 hours.

Note that F for many oral sustained-release theophylline preparations is 1.

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2. Williams DN, Bourdet SV. Chronic obstructive pulmonary disease. In DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed., www.accesspharmacy.com
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Discussion Points

D-1. Assume MA in Case 1 is a 64-year-old man with significant liver disease due to alcoholism and has severe COPD. How would these factors affect the maintenance dose you calculated for him?

D-2. In Case 2, assume CJ does not smoke tobacco, but is started on ciprofloxacin for her bronchitis. How would these changes affect her aminophylline maintenance dose?

D-3. If SR in Case 3 had a serum theophylline level of 16.2 mcg/mL as a result of his theophylline continuous infusion maintenance dose, what dose of oral sustained-release theophylline administered every 8 hours would he need to achieve a steady-state average plasma concentration of 12 mcg/mL?

D-4. Based on your experience in the provision of direct patient care, design a pharmacy-managed theophylline/aminophylline dosing protocol that could be used in your practice setting. This protocol should be written from the standpoint that the pharmacist is providing complete dosing and monitoring of theophylline/aminophylline in a patient case (instead of simply providing recommendations to a physician to manage). All steps (including equations used) required to effectively dose and monitor a patient for which theophylline/aminophylline is prescribed should be included. Describe in detail how you would monitor this drug using serum concentrations. Write the order for this drug as it would appear in the Physician's Order section of the patient's medical record.

D-5. Assume that a 49-year-old female, 5' 8" and 162 lbs, with a serum creatinine of 1.26 mg/dL, and white blood cell count of 18,300/mm^3, is receiving aminophylline as a continuous infusion in the dose of 38 mg/hour. This dose was initiated at 8 AM on 12/1. Describe in detail how you would determine when a serum level (and what type of level) should be obtained. Then write an order as it would appear in the Physician's Order section of the patient's medical record for how the serum level should be obtained. This order should be grammatically correct, include only approved abbreviations, and provide sufficient detail so that nursing services can easily follow your instructions without having to contact you for further clarification.

LESSON 15
Phenytoin and Digoxin

Phenytoin

Phenytoin is an anticonvulsant medication used for many types of seizure disorders. Phenytoin is usually administered either orally or intravenously and exhibits nonlinear, or Michaelis–Menten, kinetics (see Lesson 10). Unlike drugs undergoing first-order elimination (**Figure 15-1**), the plot of the natural logarithm of concentration versus time is nonlinear with phenytoin (**Figure 15-2**). Phenytoin is 90% protein bound; only the unbound fraction is active. (Note that patients with low serum albumin concentrations will have a higher unbound, or active, fraction of phenytoin. This should be factored in when dosing these patients.)

Phenytoin is metabolized by hepatic enzymes that can be saturated with the drug at concentrations within the therapeutic range. Consequently, as the phenytoin dose increases, a disproportionately greater increase in plasma concentration is achieved. This enzyme saturation process can be characterized with an enzyme-substrate model first developed by the biochemists Michaelis and Menten in 1913. In this metabolic process, drug clearance is constantly changing (in a nonlinear fashion) as dose changes. Drug clearance decreases as drug concentration increases (**Figures 15-3** and **15-4**).

To describe the relationship between concentration and dose, a differential equation can be written as shown below:

$$\frac{dX}{dt} = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

where:

- dX = change in amount of drug;
- dt = change in time;
- V_{max} = maximum amount of drug that can be metabolized per unit time, usually expressed as milligrams per day;
- K_m = Michaelis–Menten constant, representing the concentration of phenytoin at which the rate of this enzyme-saturable hepatic metabolism is one-half of maximum; and
- C_{ss} = average steady-state phenytoin concentration.

Next, this differential equation can be re-expressed algebraically by assuming that we are at steady state and dX/dt is held constant. Then dX/dt, the change in the

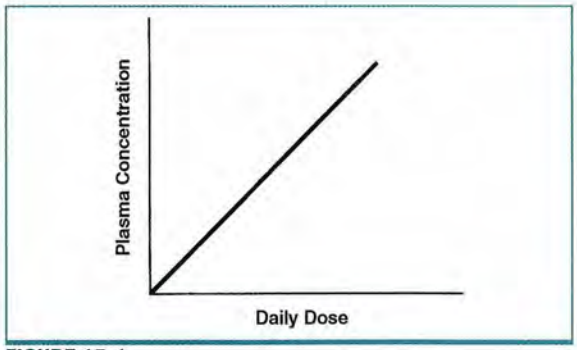

FIGURE 15-1.
First-order elimination model.

amount of drug (X) over time (t), can be expressed as X_0/τ (dose over dosing interval), as shown in the following equation:

$$(X_0/\tau)(S) = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1.**)

where:

X_0/τ = amount of phenytoin free acid divided by dosing interval (which can also be expressed as X_d, meaning daily dose of phenytoin free acid) and

S = the salt factor or the fraction of phenytoin free acid in the salt form used. S equals 0.92 for phenytoin sodium injection and capsules and 1.0 for phenytoin suspension and chewable tablets (i.e., the free acid form of phenytoin), and 0.66 for fosphenytoin injection. The oral bioavailability of phenytoin is considered to be 100%, so an F factor is not needed in these calculations.

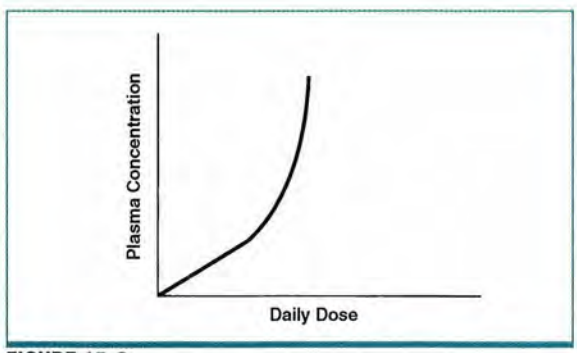

FIGURE 15-2.
Michaelis–Menten elimination model.

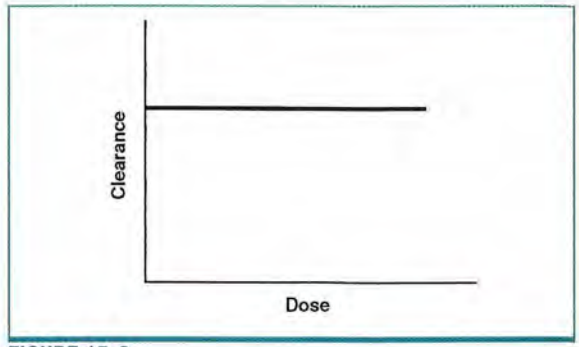

FIGURE 15-3.
First-order elimination model.

Clinical Correlate

Although fosphenytoin is a pro-drug containing only 66% phenytoin free acid, it is correctly prescribed and labeled in units of *PE*, meaning phenytoin sodium equivalents. The commercial fosphenytoin product is packaged to be very similar to phenytoin sodium injection; it contains 150-mg fosphenytoin per 2-mL ampule, providing 100 mg PE (100-mg phenytoin sodium equivalents). Fosphenytoin is readily transformed to phenytoin free acid by various phosphatases throughout the body.

This Michaelis–Menten equation (MME) can then be rearranged to solve for C_{ss} as follows:

$$(X_0/\tau)(S) = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1.**)

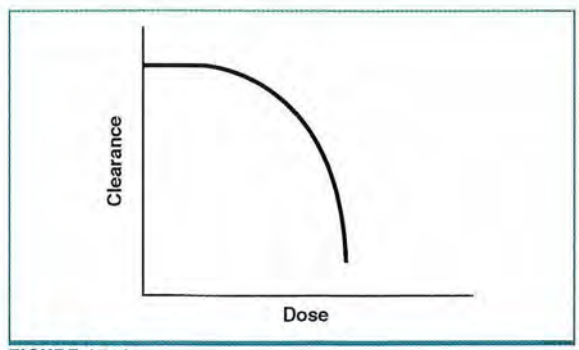

FIGURE 15-4.
Michaelis–Menten elimination model.

First, cross-multiply by the denominator:

$$[(X_0/\tau)(S) \times K_m] + [(X_0/\tau)(S) \times C_{ss}] = V_{max} \times C_{ss}$$

Then transpose $[(X_0/\tau)(S) \times C_{ss}]$ to the right side of the equation:

$$[(X_0/\tau)(S) \times K_m] = [V_{max} \times C_{ss}] - [(X_0/\tau)(S) \times C_{ss}]$$

Factor out C_{ss}:

$$[(X_0/\tau)(S) \times K_m] = C_{ss}[V_{max} - (X_0/\tau)(S)]$$

Transpose $[V_{max} - (X_0/\tau)(S)]$ to the left side of the equation:

$$C_{ss} = \frac{(X_0/\tau)(S) \times K_m}{V_{max} - (X_0/\tau)(S)}$$

The two representations of the MME below can now be used for phenytoin dosing, as illustrated in the following cases:

$$(X_0/\tau)(S) = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

15-1 $$C_{ss} = \frac{(X_0/\tau)(S) \times K_m}{V_{max} - (X_0/\tau)(S)}$$

Phenytoin Pharmacokinetic Parameters

In contrast to first-order drugs that use pharmacokinetic parameters for K and V, phenytoin dose calculations use population estimates for K_m and V_{max}. A K_m population estimate of 4 mg/L and a V_{max} estimate of 7 mg/kg/day are commonly used. Note, however, that K_m can range from 1 to 15 mg/L while V_{max} can range from 3 to > 10 mg/kg/day in selected patients. Phenytoin's volume of distribution is usually estimated as 0.65 L/kg total body weight. Last, phenytoin trough serum drug concentrations (meaning in this case, at least 8 to 12 hours after last oral dose) are usually used in dosing adjustment calculations to avoid unpredictable rates and extent of drug absorption from various dosage forms.

CASE 1

SG, a 42-year-old black man, is admitted to the hospital with status epilepticus that was successfully treated with intravenous lorazepam. His physician has written an order for the pharmacy to calculate and order an IV phenytoin loading dose, recommend an initial oral maintenance dose, and order timing of plasma concentrations. Other pertinent clinical data include weight, 75 kg; height, 5' 8"; serum creatinine, 1.2 mg/dL; and serum albumin, 4.8 g/dL.

Problem 1A. What intravenous loading dose and oral maintenance dose would you recommend to achieve and maintain a phenytoin concentration of approximately 20 mg/L?

Calculation of the loading dose is not affected by the nonlinear pharmacokinetics of multiple-dose phenytoin regimens. The loading dose calculation is based on the patient's weight, estimated volume of distribution, serum albumin concentration, renal function assessment, and the salt form (i.e., salt factor) of phenytoin used. The generally accepted population parameter for phenytoin's volume of distribution is 0.65 L/kg of body weight. The loading dose (X_0) formula is:

$$X_0 = \frac{V \times C_{desired}}{S}$$

(See **Equation 1-1**.)

where:

V = volume of distribution estimate of 0.65 L/kg [V = 0.65 L/kg (75 kg) = 48.8 L for SG],

$C_{desired}$ = concentration desired 1 hour after the end of the infusion (20 mg/L for SG), and

S = salt factor (0.92 for injection). Note that this dose falls within the empiric loading dose range of 15–20 mg/kg.

Therefore:

$$X_0 = \frac{(48.8\ \text{L})(20\ \text{mg/L})}{0.92}$$

$$= 1060\ \text{mg of phenytoin sodium or fosphenytoin PE injection}$$

We could then order a dose of 1000 mg of phenytoin mixed in 100 mL of normal saline given intravenously via controlled infusion. The administration rate for phenytoin sodium injection should not exceed 50 mg/minute to avoid potential cardiovascular toxicity associated with the propylene glycol diluent of the phenytoin injection. The accuracy of this loading dose estimate can be checked by obtaining a phenytoin plasma drug concentration approximately 1 hour after the end of the loading dose infusion. Alternatively, we could give this 1000 mg of phenytoin sodium as the fosphenytoin salt (Cerebyx®) also at a dose of 1000 mg PE (i.e, *p*henytoin sodium *e*quivalents) of fosphenytoin at a rate of 150 mg/min. Both doses will deliver the same amount (920 mg) of phenytoin free acid.

Clinical Correlate

Phenytoin sodium injection uses a propylene glycol base as its vehicle and will precipitate in most IV fluids. It is most compatible in normal saline but can even precipitate in this fluid and clog an existing inline IV filter if one is being used. Propylene glycol is a cardiotoxic agent and can cause various complications, such as bradycardia and hypotension. An alternative is to use the newer fosphenytoin injection, which is compatible with many IV fluids and can also be administered safely at a faster rate (up to 150 mg/minute).

Maintenance Dose Calculations

Several methods to calculate maintenance dose are described, with each method requiring more serum drug concentrations and yielding more accurate dosing estimates. Phenytoin dosage adjustments using these methods are more commonly done in the outpatient setting because they require steady-state concentrations that may take more than 2 weeks to be attained.

There are two methods to calculate an initial daily maintenance dose (X_d): an empiric method and a method based on estimating the patient's V_{max} and K_m.

Clinical Correlate

The **Phenytoin Cheat Sheet** at the end of the Maintenance Dose Calculations section is a concise review of the equations and sequencing for the three dose calculation methods.

Method 1A (Empiric)

Multiply SG's weight of 75 kg by 5 mg/kg/day to get an estimated dose of 375 mg of phenytoin free acid or 408 mg of phenytoin sodium, which would be rounded to 400 mg. This dose of 400 mg/day may be divided into 200 mg twice daily, if necessary, to decrease the likelihood of enzyme saturation and reduce concentration-dependent side effects. This assumes that the patient has an average K_m and V_{max}.

Method 1B (Population Parameters)

Substitute population estimates for V_{max} and K_m into the MME and solve for the dose as follows:

$$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

Therefore:

$$X_d(0.92) = \frac{525 \text{ mg/day} \times 15 \text{ mg/L}}{4 \text{ mg/L} + 15 \text{ mg/L}}$$

$$= \frac{7875 \text{ mg}^2\text{L/day}}{19 \text{ mg/L}}$$

$$= 415 \text{ mg/day of phenytoin free acid}$$

$$X_d = \frac{415 \text{ mg/day}}{0.92}$$

$$= 451 \text{ mg/day of the sodium salt of phenytoin,}$$

rounded to 450 mg/day

where:

V_{max} = population estimate of maximum rate of drug metabolism (7 mg/kg/day × 75 kg = 525 mg/day),

K_m = population estimate of Michaelis–Menten constant (4 mg/L),

C_{ss} = desired average steady-state plasma concentration of 15 mg/L, and

S = salt factor (0.92 for phenytoin sodium capsules).

Note how the units in the equation cancel out, yielding mg/day as the final units.

This calculation of 415 mg of phenytoin free acid is larger than our empiric estimate of 375 mg/day, showing that the empiric method of 5 mg/kg/day results in a lower value for SG's initial phenytoin maintenance dose. In SG's case, although this would equal a daily dose of four 100-mg phenytoin sodium capsules plus one 50-mg phenytoin tablet (which is phenytoin free acid), a patient would usually be started on 400 mg/day (200 mg BID) and titrated up to 450 mg if needed based on plasma phenytoin drug concentrations.

Problem 1B. When would you recommend that steady-state plasma concentrations be drawn?

It is difficult to calculate when multiple dosing with phenytoin will reach steady state because the time to steady state is concentration dependent. With drugs that undergo first-order elimination, steady state can be reached in three to five drug half-lives because this model assumes that clearance and volume of distribution are constant. However, because of its capacity-limited metabolism, phenytoin clearance decreases with increasing concentration. Therefore, the calculation of time to reach steady state is quite complicated and cannot be based on half-life. In fact, phenytoin does not have a true half-life; its half-life is dependent on drug concentration.

The major factor in determining how long it will take to attain steady state is the difference between V_{max} and the daily dose. The closer V_{max} is to the dose, the longer it will take to achieve steady state. This relationship between V_{max} and concentration can be derived mathematically by examining the equations used to calculate dose for first- and zero-order models. We will start by rearranging two definitions in the first-order model:

$$C_{ss} = \frac{X_0}{V} \quad \text{rearranges to} \quad X_0 = C_{ss} \times V$$

(See **Equation 1-1.**)

And

$$Cl_t = VK \quad \text{rearranges to} \quad V = \frac{Cl_t}{K}$$

so, by substituting for V:

$$X_0 = \frac{C_{ss} \times Cl_t}{K} \quad \text{or} \quad X_0 \times K = C_{ss} \times Cl_t$$

$C_{ss} \times Cl_t$ from our first-order equation can be substituted for X_0/τ in the zero-order equation derived in the introduction:

$$X_0/\tau = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1.**)

Substituting $C_{ss} \times Cl_t$ for X_0/τ yields:

$$Cl_t \times C_{ss} = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

Solving for Cl_t:

$$(C_{ss} \times Cl_t \times K_m) + (Cl_t \times C_{ss}^2) = V_{max} \times C_{ss}$$

$$\frac{C_{ss} \times Cl_t \times K_m}{C_{ss}} + \frac{Cl_t \times C_{ss}^2}{C_{ss}} = V_{max}$$

$$(Cl_t \times K_m) + (Cl_t \times C_{ss}) = V_{max}$$

$$Cl_t (K_m + C_{ss}) = V_{max}$$

This equation can now be rearranged to represent clearance in terms of V_{max} and C_{ss} as shown:

$$Cl_t = \frac{V_{max}}{K_m + C_{ss}}$$

where:

Cl_t = clearance of phenytoin;

V_{max} = maximum rate of drug metabolism, usually expressed as milligrams per day,

K_m = Michaelis–Menten constant, representing the concentration of phenytoin at which the rate of this enzyme-saturable hepatic metabolism is half of maximum, and

C_{ss} = average steady-state phenytoin concentration.

Examination of this equation shows that when C_{ss} is very small compared to K_m, Cl_t will approximate V_{max}/K_m, a relatively constant value. Therefore, at low concentrations, the metabolism of phenytoin follows a first-order process. However, as C_{ss} increases to exceed K_m, as is usually seen with therapeutic concentrations of phenytoin, Cl_t will decrease and metabolism will convert to zero order. We can calculate an estimate of the time it takes to get to 90% of steady state using the following equation:

$$t_{90\%} = \frac{K_m \times V}{(V_{max} - X_d)^2}\left[(2.3 \times V_{max}) - (0.9 \times X_d)\right]$$

(See **Equation 10-4.**)

where:

$t_{90\%}$ = estimated number of days to get to 90% of steady state,

X_d = daily dose of phenytoin (in mg/day),

V = volume of distribution,

V_{max} = maximum rate of drug metabolism (in milligrams per day), and

K_m = Michaelis–Menten constant.

This equation is derived from a complex integration of the differential equation describing the difference between the rate of drug coming in (i.e., the daily dose) and the rate of drug going out of the body. This equation gives us an estimate of when to draw steady-state plasma concentrations and is based on the assumption that the beginning phenytoin concentration is zero. In patients such as SG, who have previously received a loading dose, $t_{90\%}$ may be different, usually shorter, unless the loading dose yielded an initial concentration greater than that desired, in which case $t_{90\%}$ would be even longer.

Clinical Correlate

The $t_{90\%}$ equation is a very rough estimate of time to 90% of steady state and should be used only as a general guide. The clinician should check nonsteady-state phenytoin concentrations before this time to avoid serious subtherapeutic or supratherapeutic concentrations.

In patient SG's case, $t_{90\%}$ is calculated as follows:

$$t_{90\%} = \frac{K_m \times V}{(V_{max} - X_d)^2}\left[(2.3 \times V_{max}) - (0.9 \times X_d)\right]$$

(See **Equation 10-4.**)

where:

K_m = 4 mg/L,

V_{max} = 7 mg/kg/day × 75 kg (525 mg/day),

X_d = 415 mg/day of phenytoin (free acid), and

V = 0.65 L/kg × 75 kg (48.8 L).

Therefore:

$$t_{90\%} = \frac{4\ \text{mg/L} \times 48.8\ \text{L}}{(525\ \text{mg/day} - 415\ \text{mg/day})^2}\left[(2.3 \times 525\ \text{mg/day}) - (0.9 \times 415\ \text{mg/day})\right]$$

$$= 0.016(834)$$

$$= 13.34\ \text{days}$$

Note how the units cancel out in this equation, leaving the answer expressed in days, not hours. This equation estimates that it will take SG approximately 14 days for his phenytoin concentration to reach steady state with a desired C_{ss} concentration of 15 mg/L.

Close inspection of this calculation illustrates the impact that the denominator—the difference of V_{max} and daily dose—has on the time it takes to reach steady state. For example, if we assume that SG's daily dose was 500 mg/day, we can re-solve the $t_{90\%}$ equation with strikeouts showing the changes.

$$t_{90\%} = \frac{4\ \text{mg/L} \times 48.8\ \text{L}}{(525\ \text{mg/day} - 500\ \text{~~415~~ mg/day})^2}\left[(2.3 \times 525\ \text{mg/day}) - (0.9 \times 500\ \text{~~415~~ mg/day})\right]$$

$$= \frac{4(48.8)}{525-500}\left[2.3(525) - 0.9(500)\right]$$

$$= \frac{195.2}{252}(1207.5 - 450)$$

$$= 0.312(757.5)$$

$$= 236.6\ \text{days}$$

This means that, theoretically, it would now take approximately 237 days for patient SG to reach steady state on a dose of 500 mg/day. Of course, SG would actually show signs of toxicity long before he reached steady state, but this illustrates the effect the difference of dose (and V_{max}, similarly) has on the calculation of time to steady state. In fact, if the daily dose exceeds V_{max}, steady state is never achieved.

CASE 2

For this case, we use the data presented in Case 1 and continue treating patient SG. A phenytoin plasma concentration (free acid) of 6 mg/L is drawn 18 days after the beginning of therapy. Although SG's seizure frequency has decreased, he is still having occasional seizures, and his physician has decided to adjust his dosing regimen to attain a plasma concentration of 15 mg/L.

Method 2 (One Steady-State Level)

Problem 2A. Calculate an appropriate dosing regimen to attain our desired concentration of 15 mg/L.

Now that we have one steady-state concentration, we can calculate a new maintenance dose for SG. This is done using the basic MME with two unknowns, V_{max} and K_m. We can use a population estimate for one of the unknowns (usually K_m), solve for the other unknown, and then recalculate the new dose once again using the MME. This method is preferred over using population estimates for both unknowns. For SG, this calculation is as follows:

$$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

First, rearrange the MME to isolate V_{max}:

$$V_{max} = \frac{(X_d \times S)(K_m + C_{ss})}{C_{ss}}$$

$$V_{max} = \frac{(415\ \text{mg/day})(4\ \text{mg/L} + 6\ \text{mg/L})}{(6\ \text{mg/L})}$$

$$= \frac{(415\ \text{mg/day})(10\ \text{mg/L})}{(6\ \text{mg/L})}$$

$$= \frac{(4150\ \text{mg}^2/\text{day} \times \text{L})}{(6\ \text{mg/L})}$$

$$= 691.67\ \text{mg/day, rounded to } 690\ \text{mg/day}$$

(See **Equation 10-1**.)

where:

V_{max} = calculated estimate of patient's V_{max},
K_m = population estimate of 4 mg/L,
$X_d \times S$ = patient's daily dose of phenytoin (415 mg/day of free acid), and
C_{ss} = reported steady-state concentration (6 mg/L).

So SG's new estimated V_{max} is 690 mg/day, which is larger than the population estimate of 525 mg/day, meaning that he has a greater phenytoin clearance than first estimated.

We now take the new V_{max} and the MME for our new dose and use it in the MME to solve for X_d as follows:

$$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

$$X_d \times S = \frac{690 \text{ mg/day} \times 15 \text{ mg/L}}{4 \text{ mg/L} + 15 \text{ mg/L}}$$

$$= \frac{10{,}455 \text{ mg}^2\text{/day} \times \text{L}}{19 \text{ mg/L}}$$

$$= 544.74 \text{ mg/day}$$

X_d (0.92) = 545 mg/day of phenytoin free acid

X_d = 587 mg/day of phenytoin sodium, rounded to 590 mg/day

where:

$X_d \times S$ = new dose of phenytoin sodium ($S = 0.92$),
C_{ss} = desired steady-state concentration of 15 mg/L,
K_m = population estimate of 4 mg/L, and
V_{max} = calculated estimate (690 mg/day).

Therefore, SG's new dose would be 590 mg/day as phenytoin sodium capsules in divided doses, which is equivalent to 545 mg of phenytoin free acid. Because this is a large increase in dose, it may saturate the patient's hepatic enzymes, causing the plasma concentration to increase disproportionately. The practitioner may decide to give a lower dose initially. Again, note how units cancel out in this equation, yielding mg/day.

Clinical Correlate

Phenytoin doses are usually increased by 25–100 mg/day. Because the clinical accuracy using this first method is not as accurate and predictive as those for the aminoglycosides and theophylline, good clinical judgment is required when recommending a dose.

Problem 2B. When should a plasma phenytoin concentration be drawn?

We can recalculate when SG's phenytoin concentration will reach steady state on this new dose. Remember, time to 90% of steady state ($t_{90\%}$) is dependent on plasma drug concentration. SG's new estimate of $t_{90\%}$ is calculated as follows:

$$t_{90\%} = \frac{K_m \times V}{(V_{max} - X_d)^2}\left[(2.3 \times V_{max}) - (0.9 \times X_d)\right]$$

(See **Equation 10-4.**)

Therefore:

$$t_{90\%} = \frac{4 \text{ mg/L} \times 48.8 \text{ L}}{(690 \text{ mg/day} - 545 \text{ mg/day})^2}$$
$$\left[(2.3 \times 690 \text{ mg/day}) - (0.9 \times 545 \text{ mg/day})\right]$$

$$= 10.18 \text{ days for new } t_{90\%} \text{ to be reached}$$

where:

K_m = population estimate (4 mg/L),
V_{max} = calculated estimate based on one steady-state concentration (697 mg/day),
X_d = daily dose of 552 mg/day of phenytoin free acid, and
V = population estimate of volume of distribution (48.8 L).

Note that our new $t_{90\%}$ is slightly smaller than the previous estimate because the difference between V_{max} and dose is now greater.

Method 3 (Two Steady-State Levels)

Problem 2C. Three weeks later, SG's plasma phenytoin concentration is 20 mg/L. He is now seizure free, and his physician wants to adjust his dose to get his plasma concentration back to 15 mg/L. Note that SG states that he has been taking his phenytoin exactly as prescribed. What dose would you now recommend to achieve a plasma phenytoin concentration of 15 mg/L?

Now that we have measured two different steady-state concentrations at two different doses, we can make an even more accurate dosing change.

As shown in Lesson 14, clearance can be expressed as X_d/C_{ss}, resulting in the plot in **Figure 15-5**.

We can now plot both steady-state doses (X_1 of 415 mg/day and X_2 of 545 mg/day) on the y-axis and both steady-state X_d/C_{ss} values (X_1/C_1 = 415/6 L/day and X_2/C_2 = 545/20 L/day) on the x-axis, thus linearizing these relationships. This

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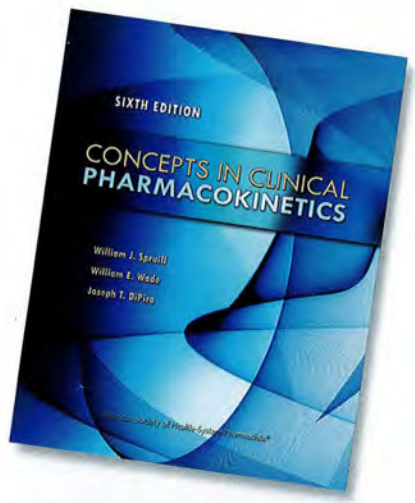

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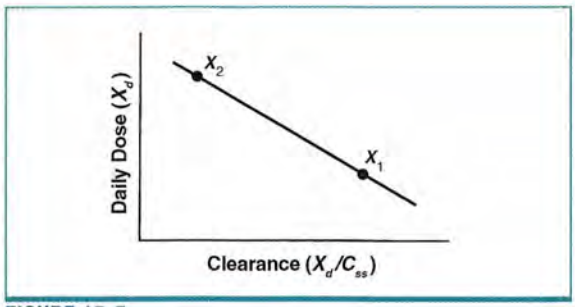

FIGURE 15-5.
Relationship of daily dose to clearance.

allows us to express the relationship in the algebraic form for a straight line, $Y = mX + b$, where m, the slope of the line, equals the negative value of the patient's K_m (i.e., $m = -K_m$) and the y-intercept is the patient's V_{max}. For SG, this graph is drawn as in **Figure 15-6**.

The slope of the line, which represents $-K_m$, can now be calculated as follows:

$$-K_m = \frac{X_1 - X_2}{\frac{X_1}{C_1} - \frac{X_2}{C_2}}$$

$$= \frac{415\ \text{mg/day} - 545\ \text{mg/day}}{\frac{415\ \text{mg/day}}{6\ \text{mg/day}} - \frac{545\ \text{mg/day}}{20\ \text{mg/day}}}$$

$$K_m = 3.10\ \text{mg/L}$$

(See **Equation 10-2.**)

Clinical Correlate

It is best to use the free acid amount of phenytoin, not the sodium salt, when calculating K_m in the above equation and in all subsequent calculations.

Next, we substitute this new value for K_m into the MME and solve for an even more accurate V_{max} than calculated previously, as follows:

$$V_{max} = \frac{(X_d \times S)(K_m + C_{ss})}{C_{ss}}$$

(See **Equation 10-1.**)

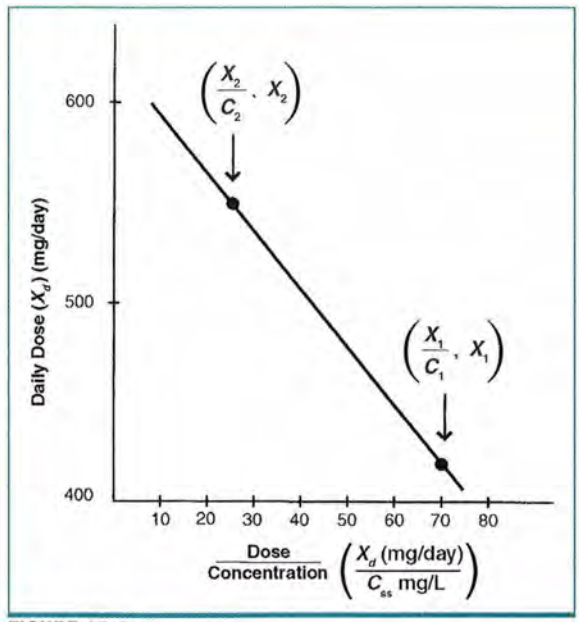

FIGURE 15-6.
Relationship of daily dose to the dose divided by steady-state concentration achieved.

where:

$X_d \times S$ = either of the doses SG received (415 or 545 mg/day of free acid),

C_{ss} = steady-state concentration at the dose selected, and

K_m = calculated value of 3.10 mg/L.

Using the 415-mg/day dose, $C_{ss} = 6$ mg/L.

$$V_{max} = \frac{(415\ \text{mg/day})(3.10\ \text{mg/L} + 6\ \text{mg/L})}{6\ \text{mg/L}}$$

$$= 629.42\ \text{mg/day}$$

Using the 545-mg/day dose, $C_{ss} = 20$ mg/L.

$$V_{max} = \frac{(545\ \text{mg/day})(3.10\ \text{mg/L} + 20\ \text{mg/L})}{20\ \text{mg/L}}$$

$$= 629.48\ \text{mg/day}$$

which we will round to 630 mg/day. Note that either set of doses and concentrations will give the same V_{max}.

Finally, we substitute our new V_{max} of 630 mg/day and our calculated K_m of 3.10 mg/mL into the MME and solve for X_d as follows:

$$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See **Equation 10-1**.)

$$X_d(0.92) = \frac{(630 \text{ mg/day})(15 \text{ mg/L})}{3.10 \text{ mg/L} + 15 \text{ mg/L}}$$

$$X_d(0.92) = 522 \text{ mg/day of phenytoin free acid}$$

$$X_d = 567.5 \text{ mg/day of phenytoin sodium}$$

where:

V_{max} = 630 mg/day of phenytoin free acid,

K_m = 3.10 mg/L,

C_{ss} = desired average steady-state plasma concentration of 15 mg/L, and

S = salt factor (0.92 for phenytoin sodium capsules).

Therefore, we could give SG 560 mg (five 100-mg phenytoin capsules plus two 30-mg phenytoin capsules) daily in divided doses. This would give slightly less than the calculated amount of 567.5 mg/day.

Clinical Correlate

It is important to dose phenytoin correctly so side effects do not occur. Dose-related side effects at serum concentrations greater than 20 mcg/mL include nystagmus, whereas concentrations greater than 30 mcg/mL may result in nystagmus and ataxia. Concentrations greater than 40 mcg/mL may produce ataxia, lethargy, and diminished cognitive function. Adverse effects that may occur at therapeutic concentrations include gingival hyperplasia, folate deficiency, peripheral neuropathy, hypertrichosis, and thickening of facial features.

Long-Term Phenytoin Monitoring

Repeated use of Method 3 (above) allows for continued dosing adjustments over many years in patients maintained on phenytoin; this is especially useful as children get older and bigger. Any two sets of drug concentrations and different dose pairs can be used to calculate an adjusted dose, which makes for interesting math when a patient has dozens of concentrations over many years. Compliance should always be assessed before trusting these dosage adjustment calculations.

Phenytoin Cheat Sheet

The Phenytoin Cheat Sheet contains the equations and sequencing for the three dosing methods detailed in the Maintenance Dose Calculations Section above. Equations are presented for calculating doses when you have no phenytoin serum drug concentration, one phenytoin serum drug concentration, and, finally, two phenytoin serum drug concentrations obtained on two different doses.

PHENYTOIN DOSING CHEAT SHEET

DOSING METHOD 1A:

Use 5 mg/kg/day

DOSING METHOD 1B:

Use population estimates for the Michaelis–Menten values for K_m of 4 mg/L and V_{max} of 7 mg/kg/day and solve the general MME formula as shown below:

Equation 1 MME:

$$X_d \times S = \frac{V_{max}(C_{ss\ (desired)})}{(K_m + C_{ss\ (desired)})}$$

K_m estimate = 4 mg/L

V_{max} estimate = 7 mg/kg/day

S = Salt form factor (either 1.0 or 0.92, or 0.66)

DOSING METHOD 2: ONE STEADY-STATE LEVEL

Use this method as in Equation 2 below after you have one steady-state phenytoin serum drug concentration to **solve for V_{max}** while still using the population parameter for K_m of 4 mg/L.

After solving for this better value for V_{max}, use it plus the old K_m value in the MME to re-solve for dose, as shown below.

To solve for V_{max}:

Equation 2:

This is simply a **rearrangement of MME (Equation 1):**

$$V_{max} = \frac{(X_d \times S)(K_m + C_{ss(lab)})}{C_{ss(lab)}}$$

To solve for dose:

Use Equation 1 again.

Equation 1 (MME) again:

$$X_d \times S = \frac{better\,V_{max}(C_{ss(desired)})}{(\text{population parameter for } K_m + C_{ss(desired)})}$$

K_m estimate = 4 mg/L

V_{max} estimate = as solved for mg/kg/day

S = Salt form factor (either 1.0 or 0.92, or 0.66)

DOSING METHOD 3: TWO STEADY-STATE LEVELS ON TWO DIFFERENT DOSES

Use after you have **two steady-state** phenytoin concentrations from two different phenytoin doses. You can now work Equation 3 to solve for **an even better value for K_m** (shown below).

Use this better K_m value to once again re-solve for a better V_{max} value than used in Method 2. Once you get new V_{max} (i.e., real K_m and V_{max}), re-solve Equation 1 (MME) again for dose.

Equation 3:

Use this to solve for real K_m:

X = dose

C = concentration

To solve for real V_{max}:

Use Equation 2 again.

To solve for dose:

Use Equation 1 (MME) again.

To solve for real V_{max}:

Use Equation 2 once again.

$$real\,V_{max} = \frac{(X_d \times S)(real\,K_m + C_{ss(lab)})}{C_{ss(lab)}}$$

To solve for dose:

Use Equation 1 again.

Equation 1 (MME) yet again:

$$best\,X_d \times S = \frac{real\,V_{max}(C_{ss(desired)})}{(real\,K_m + C_{ss(desired)})}$$

real K_m (mg/L)

real V_{max} (mg/kg/day)

S = Salt form factor (either 1.0 or 0.92, or 0.66)

Digoxin

Digoxin is an inotropic medication that may be useful in the treatment of patients with heart failure (HF) to decrease hospitalizations due to this disorder. Desired serum concentrations in these patients range from 0.5 to 0.9 ng/mL.[1] This conservative target has been associated with a decline in the overall incidence of digoxin toxicity. Notice that the units of plasma concentrations for digoxin are different (nanograms per milliliter) from those of other commonly monitored drugs (usually milligrams per liter).

Digoxin may also be used in the management of arrhythmias such as atrial fibrillation (AF) and atrial flutter. It is effective in controlling heart rate at rest in patients with AF and may be used in patients with concomitant heart failure, left ventricular dysfunction, and a sedentary lifestyle. Digoxin is an acceptable treatment for slowing a rapid ventricular response and improving left ventricular function in patients with acute myocardial infarction and AF associated with severe left ventricular dysfunction and HF. In combination with a beta-blocker or nondihydropyridine calcium channel antagonist, digoxin may be used to control heart rate during exercise in patients with AF, as well as in the pregnant patient with AF. Digoxin may also be used to terminate paroxysmal supraventricular tachycardia (PSVT).[2,3]

In patients with normal left ventricular function, digoxin is less effective for ventricular rate control than calcium channel blockers or beta-blockers. However, it may be used in combination with these agents in patients with less than satisfactory ventricular rate control from monotherapy.[3]

Doses of digoxin are usually administered orally or intravenously. Loading doses are no longer recommended in HF patients.[1] Although digoxin loading doses have been used extensively in patients with AF, atrial flutter, and PSVT, other drugs are more effective and/or have a more rapid onset of action. Therefore, digoxin loading doses are rarely needed unless alternative therapy is contraindicated or not effective in a given patient.[2] The current recommended loading dose of digoxin for ventricular rate control is 0.25 mg IV every 2 hours up to a total of 1.5 mg. For PSVT, the loading dose is 8–12 mcg/kg given as follows: one-half of the dose is given over 5 minutes; 25% is given in 4 to 8 hours; and the final 25% given 4 to 8 hours later.[3] Electrocardiogram monitoring is performed during loading dose administration to assess for toxicity.[4] The recommended maintenance dose of digoxin for ventricular rate control is 0.125 to 0.375 mg per day. With declining renal function, these doses may be further reduced or administered as alternate day therapy.[3]

Steady-state volume of distribution (V_{ss}) of digoxin is large and extremely variable. Differences in renal function account for some of the interpatient variation.

15-2 V_{ss} = 4 to 9 L/kg ideal body weight (IBW) (average adult, 7 L/kg IBW)[4]

When calculating an oral digoxin dose, the bioavailability (F) of the dosage form used must be considered. For patients with normal oral absorption, digoxin tablets are 50–90% (average, 70%) absorbed (F = 0.7), and digoxin elixir is 75–85% absorbed (average, F = 0.8).

Systemic clearance (Cl_t) of digoxin can be calculated as follows[5]:

15-3 $$Cl_t = (1.303 \times CrCl) + Cl_m$$

where:

Cl_m = metabolic clearance.
= 40 mL/min for patients with no or mild HF
= 20 mL/min for patients with moderate to severe HF

Several methods have been proposed for calculating doses of digoxin that have been described in detail elsewhere. Recent investigators have developed a nomogram for determining digoxin doses that achieve lower serum concentrations.[6]

CASE 3

TS is a 72-year-old, 5' 5'', 125-lb female who has a diagnosis of HF for which she currently receives a beta-blocker, an angiotensin-converting enzyme inhibitor (ACEI), and a diuretic. She has been hospitalized three times in the past year for her HF; at this time, her physician wishes to initiate digoxin therapy. Her current serum creatinine is 1.00 mg/dL.

Problem 3A. Calculate a maintenance dose of digoxin tablets to be given to TS to achieve a satisfactory steady-state serum digoxin level.

Clinical Correlate

Patients with HF usually do not require a loading dose of digoxin before initiating maintenance dose therapy.[1]

The relationship between the steady-state plasma concentration, maintenance dose, and total systemic clearance is shown below:

15-4 $$C_{ss} = \frac{X_d \times 10^6 \times F}{Cl_t \times \tau}$$

(See **Equation 4-3.**)

The above equation can be rearranged and written as follows:

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

where:

- X_d = maintenance dose of digoxin, in milligrams per day,
- C_{ss} = steady-state plasma concentration, in nanograms per milliliter,
- Cl_t = total body clearance,
- τ = dosing interval, in minutes (1440 minutes = 1 day),
- 10^6 = conversion from nanograms to milligrams (i.e., 10^6 ng = 1 mg), and
- F = 0.7 for tablets.

We have previously established that the desired steady-state serum digoxin concentration in the patient with HF ranges from 0.5 to 0.9 ng/mL. We will choose a level of 0.8 ng/mL for TS.

To determine systemic clearance, we must first estimate TS's creatinine clearance. We use the Cockcroft–Gault equation:

$$CrCl_{(female)} = (0.85)\frac{(140 - age)(IBW)}{72 \times SCr}$$

(See **Equation 9-1.**)

where:

- CrCl = creatinine clearance, in milliliters per minute;
- IBW = ideal body weight, in kilograms; and
- SCr = serum creatinine, in milligrams per deciliter.

Therefore:

$$CrCl_{(female)} = \frac{(0.85)(140 - 72)(57\ kg)}{72 \times 1.00}$$

$$= 46\ mL/min$$

Total body clearance of digoxin would be:

$Cl_t = (1.303 \times CrCl) + Cl_m$ (See **Equation 15-3.**)

$$= (1.303 \times 46\ mL/min) + 20\ mL/min$$

$$= 80\ mL/min$$

The daily maintenance dose required to achieve a steady-state concentration of 0.8 ng/mL would be:

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

$$X_d = \frac{0.8\ ng/mL \times (80\ mL/min) \times 1440\ min}{10^6\ ng/mg \times 0.7}$$

$$= 0.13\ mg$$

(See **Equation 15-4.**)

Therefore, TS should receive 0.125 mg of digoxin daily to achieve a steady-state digoxin concentration of slightly less than 0.8 ng/mL.

Problem 3B: Two months later, TS has a steady-state serum digoxin level drawn. The laboratory reports this value as 0.52 ng/mL. Although this value is within the thearapeutic range for HF, TS's physician desires to increase the dose to achieve a slightly higher serum concentration. Calculate a new maintenance dose for TS that will achieve a serum concentration of 0.8 ng/mL.

The first step to solving this problem is to calculate TS's actual serum digoxin clearance. We can do this as follows:

$$Cl_t = \frac{X_d \times 10^6 \times F}{C_{ss} \times \tau}$$

where:

- Cl_t = total body clearance,
- X_d = maintenance dose of digoxin, in milligrams per day,
- C_{ss} = steady-state plasma concentration, in nanograms per milliliter,
- τ = 1440 minutes (1 day),
- 10^6 = conversion from nanograms to milligrams (i.e., 10^6 ng = 1 mg), and
- F = bioavailability (0.7 for digoxin tablets).

Plugging in our values for patient TS:

$$Cl_t = \frac{0.125 \text{ mg} \times 10^6 \text{ ng/mg} \times 0.7}{0.52 \text{ ng/mL} \times 1440 \text{ min}}$$

$$= 117 \text{ mL/min}$$

From this we see that TS's total body clearance of digoxin is slightly higher than the value we calculated using population estimates.

Now, we can use this clearance value to calculate a new maintenance dose to achieve our desired serum concentration of 0.8 ng/mL.

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

$$X_d = \frac{0.8 \text{ ng/mL} \times (117 \text{ mL/min}) \times 1440 \text{ min}}{10^6 \text{ ng/mg} \times 0.7}$$

$$= 0.19 \text{ mg}$$

This dose can be achieved by alternating 0.25 mg with 0.125 mg every other day. This would be the equivalent of administering 0.1875 mg per day.

Problem 3C: TS begins her new digoxin regimen. Three months later she reports to her physician's office complaining of nausea and vomiting. A serum digoxin level (10 hours after her last dose) and serum creatinine are drawn. Her digoxin concentration is 1.6 ng/mL and her serum creatinine has risen to 1.92 mg/dL. Her physician tells JS to hold her digoxin for the next two days and come back to the office to have her serum digoxin concentration repeated. Her serum level (48 hours after the last serum level was drawn) is now 1.1 ng/mL. Calculate a new digoxin dose that will achieve a steady-state serum concentration of 0.8 ng/mL.

TS appears to now be experiencing declining renal function (rise in serum creatinine). To determine a new dose, we must first calculate her actual Cl_t. As before, we can do this by rearranging the following equation:

$$C_{ss} = \frac{X_d \times 10^6 \times F}{Cl_t \times \tau}$$

(See **Equation 15-4.**)

to:

$$Cl_t = \frac{X_d \times 10^6 \times F}{C_{ss} \times \tau}$$

where:

- Cl_t = total body clearance,
- X_d = maintenance dose of digoxin, in milligrams per day,
- C_{ss} = steady-state plasma concentration, in nanograms per milliliter,
- τ = 1440 minutes (1 day),
- 10^6 = conversion from nanograms to milligrams (i.e., 10^6 ng = 1 mg), and
- F = bioavailability (0.7 for digoxin tablets).

Plugging in our values for patient TS:

$$Cl_t = \frac{0.1875 \text{ mg} \times 10^6 \text{ ng/mg} \times 0.7}{1.6 \text{ ng/mL} \times 1440 \text{ min}}$$

$$= 57 \text{ mL/min}$$

In making this determination, it is important that we use the average daily dose TS is receiving as well as the serum value resulting from this dose (and not the serum value reported 2 days later with doses held). It is of interest to note a significant decline in digoxin total body clearance with declining renal function.

Then we use patient TS's actual Cl_t to calculate the appropriate dose to achieve our desired C_{ss} of 0.8 ng/mL.

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

$$X_d = \frac{0.8 \text{ ng/mL} \times (57 \text{ mL/min}) \times 1440 \text{ min}}{10^6 \text{ ng/mg} \times 0.7}$$

$$= 0.094 \text{ mg/day}$$

This dose can be achieved by alternating 0.125 mg with 0.0625 mg (one-half of a 0.125-mg tablet) every other day.

Problem 3D. How much longer do we need to wait until we can begin TS's new digoxin maintenance dose?

Since TS's latest serum digoxin concentration is elevated (1.1 ng/mL), we cannot begin her new maintenance dose until this value decreases to approximately 0.8 ng/mL. To calculate the amount of time that must elapse until this occurs, we can use the following equation:

$$C_{\text{level 2(steady state)}} = C_{\text{level 1(steady state)}} e^{-Kt}$$

where:

$C_{\text{level 2(steady state)}}$ = the serum concentration we desire before the new maintenance dose is started (0.8 ng/mL),

$C_{\text{level 1(steady state)}}$ = the serum concentration the patient currently has (1.1 ng/mL),

K = the elimination rate constant, and

t = the time we must wait until $C_{\text{level 2(steady state)}}$ is reached.

We can calculate K as follows:

$$K = \frac{\ln 1.1 - \ln 1.6}{48 \text{ hr}}$$

$$= 0.008 \text{ hr}^{-1}$$

Now, we can solve for time t:

$$C_{\text{level 2(steady state)}} = C_{\text{level 1(steady state)}} e^{-Kt}$$

$$0.8 \text{ ng/mL} = 1.1 \text{ ng/mL } e^{-0.008t}$$

$$0.727 = e^{-0.008t}$$

$$\ln 0.727 = \ln e^{-0.008t}$$

$$-0.319 = -0.008t$$

$$39.9 \text{ hr} = t$$

So we need to wait another 40 hours before we begin TS's new digoxin maintenance dose.

CASE 4

HK is a 56-year-old, 6' 6'' tall, 200-lb patient with HF. He is currently receiving a beta-blocker and an ACEI. His physician wishes to add digoxin to this regimen. His current serum creatinine is 1.1 mg/dL.

Problem 4A. Calculate a maintenance dose of digoxin tablets that will achieve a steady-state serum concentration of 0.7 ng/mL for HK.

The first step in solving this problem is to determine HK's total body clearance for digoxin. To determine this, we must first estimate his creatinine clearance.

$$CrCl_{male} = \frac{(140 - \text{age})(\text{IBW})}{72 \times \text{SCr}}$$

(See **Equation 9-1**.)

where:

CrCl = creatinine clearance, in milliliters per minute,

IBW = ideal body weight, in kilograms, and

SCr = serum creatinine, in milligrams per deciliter.

Therefore:

$$CrCl_{male} = \frac{(140 - 56)(91 \text{ kg})}{72 \times 1.1}$$

$$= 97 \text{ mL/min}$$

Total body clearance of digoxin would be:

$$Cl_t = (1.303 \times CrCl) + Cl_m \quad \text{(See \textbf{Equation 15-3.})}$$

$$= (1.303 \times 97 \text{ mL/min}) + 40 \text{ mL/min}$$

$$= 166.4 \text{ mL/min}$$

The daily maintenance dose required to achieve a steady-state concentration of 0.7 ng/mL would be:

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

$$X_d = \frac{0.7 \text{ ng/mL} \times (166.4 \text{ mL/min}) \times 1440 \text{ min}}{10^6 \text{ ng/mg} \times 0.7}$$

$$= 0.24 \text{ mg}$$

(See **Equation 15-4.**)

Therefore, HK should receive 0.25 mg of digoxin daily.

Problem 4B. Suppose HK had to initially receive his daily digoxin maintenance dose by IV administration. Calculate this dose.

$$X_d = \frac{C_{ss} \times Cl_t \times \tau}{10^6 \times F}$$

$$X_d = \frac{0.7 \text{ ng/mL} \times (166.4 \text{ mL/min}) \times 1440 \text{ min}}{10^6 \text{ ng/mg} \times 1}$$

$$= 0.17 \text{ mg}$$

Notice $F = 1$ for intravenously administered drugs.

Clinical Correlate

IV administration of digoxin should be given by slow IV push. This method of administration prevents the propylene glycol contained in this formulation from causing cardiovascular collapse.

Problem 4C. HK is currently receiving digoxin 0.25 mg orally daily. He has a steady-state serum digoxin level reported as 1.2 ng/mL. If all doses are held, predict how long it will take for his serum concentrattion to fall to 0.7 ng/mL.

In problem 3C, we encountered a similar situation in which we solved for the time to wait before an elevated serum concentration declined to an acceptable value with doses held. In that situation, we had two steady-state serum concentrations to solve for a K value. In the current problem, we will address how we can estimate a K value and, therefore, time to wait, with only one steady-state serum concentration available.

The first step to solving this problem is to calculate HK's actual serum digoxin clearance. We can do this as follows:

$$Cl_t = \frac{X_d \times 10^6 \times F}{C_{ss} \times \tau}$$

where:

- Cl_t = total body clearance;
- X_d = maintenance dose of digoxin, in milligrams per day;
- C_{ss} = steady-state plasma concentration, in nanograms per milliliter;
- τ = 1440 minutes (1 day);
- 10^6 = conversion from nanograms to milligrams (i.e., 10^6 ng = 1 mg); and
- F = bioavailability (0.7 for digoxin tablets).

Plugging in our values for patient HK:

$$Cl_t = \frac{0.25 \text{ mg} \times 10^6 \text{ ng/mg} \times 0.7}{1.2 \text{ ng/mL} \times 1440 \text{ min}}$$

$$= 101 \text{ mL/min}$$

Step 2 to solving this problem is to use the equation below to calculate time to wait:

$$C_{\text{level 2(steady state)}} = C_{\text{level 1(steady state)}} e^{-Kt}$$

where:

- $C_{\text{level 2(steady state)}}$ = the serum concentration we desire before the new maintenance dose is started (0.7 ng/mL),
- $C_{\text{level 1(steady state)}}$ = the serum concentration the patient currently has (1.2 ng/mL),
- K = the elimination rate constant, and
- t = the time we must wait until $C_{\text{level 2(steady state)}}$ is reached.

To be able to use this equation requires that we know the value for *K*.

We can estimate this from the following equation:

$$K = \frac{Cl}{V}$$

We can estimate *V* as 7 L/kg IBW. (See **Equation 15-2.**)

$$V = 7 \text{ L/kg} \times 91 \text{ kg}$$
$$= 637 \text{ L}$$

Now, we can estimate *K*.

K is in units of hr^{-1}

V is in units of liters

Cl therefore must be converted to units of liters per hour (L/hr):

$$101 \text{ mL/min} \times 60 \text{ min/hour} = 6060 \text{ mL/hr}$$

$$6060 \text{ mL/hr divided by } 1000 \text{ mL/L} = 6.06 \text{ L/hr}$$

$$K = \frac{Cl}{V}$$
$$= \frac{6.06 \text{ L/hr}}{637 \text{ L}}$$
$$= 0.0095 \text{ hr}^{-1}$$

Using the equation:

$$C_{\text{level 2(steady state)}} = C_{\text{level 1(steady state)}} e^{-Kt}$$
$$0.7 \text{ ng/mL} = 1.2 \text{ ng/mL } e^{-0.0095t}$$
$$0.583 = e^{-0.0095t}$$
$$\ln 0.583 = \ln e^{-0.0095t}$$
$$-0.54 = -0.0095t$$
$$56.8 \text{ hr} = t$$

So we must wait an additional 57 hours for HK's serum digoxin level to drop to 0.7 ng/mL. Before initiating a new maintenance dose, it would be prudent to repeat a serum digoxin level to ensure his elimination rate has not changed during this waiting period and that his serum concentration is an acceptable value.

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Discussion Points

Phenytoin

D-1. Suppose SG in Case 1, Problem 1A was 65 years old, weighed 95 kg, and had a serum albumin level of 2.4 mg/L. What would be his oral maintenance dose of phenytoin based on these changes?

D-2. Based on your calculations in Discussion Point 1, calculate a new maintenance dose for SG that would result in a steady-state plasma concentration of 15 mg/L.

D-3. The laboratory reports a serum phenytoin concentration of 19 mg/L from the dose you calculated in Discussion Point 2. Calculate a new dose that will result in a serum concentration of 15 mg/L (i.e., use Method 2).

D-4. Based on your experience in the provision of direct patient care, design a pharmacy-managed phenytoin dosing protocol that could be used in your practice setting. This protocol should be written from the standpoint that the pharmacist is providing complete dosing and monitoring of phenytoin in a patient case (instead of simply providing recommendations to a physician to manage). All steps required (including equations used) to effectively dose and monitor a patient for whom phenytoin is prescribed should be included. Describe in detail how you would monitor this drug using serum concentrations. Write the order for this drug as it would appear in the Physician's Order section of the patient's medical record.

D-5. A 41-year-old female, 5' 6" and 148 lbs, presents to the emergency department with uncontrolled seizures (serum creatinine, 1.2 mg/dL; serum albumin, 4.3 g/dL; white blood cell count 18,300/mm^3, receiving phenytoin 300 mg daily at home). Assuming that phenytoin 200 mg every 12 hours orally is initiated at 8 a.m. on 12/1, describe in detail the process for how you determine when serum levels (and what type of levels) should be obtained. Then write an order as it would appear in the Physician's Order section of the patient's medical record for how serum levels should be obtained. This order should be grammatically correct, include only approved abbreviations, and provide sufficient detail that nursing services can easily follow your instructions without having to contact you for further clarification.

Digoxin

D-6. Suppose TS's serum digoxin concentration in Problem 3B had been 1.1 ng/mL. What maintenance dose would be required to achieve a serum concentration of 0.8 ng/mL?

D-7. Explain how to administer an appropriate digoxin loading dose to a patient with atrial fibrillation.

APPENDIX A
Basic and Drug-Specific Pharmacokinetic Equations

Basic Pharmacokinetic Equations

Equation Showing the Relationship of Drug Concentration (mg/L), Drug Dose (mg), and Volume of Distribution (Liters)

1-1 $$\text{concentration} = \frac{\text{amount of drug in body}}{\text{volume in which drug is distributed}}$$

$$C = \frac{X}{V}$$

(See p. 10.)

Equation for Calculating Total Body Clearance

2-1 $$Cl_t = Cl_r + Cl_m + Cl_b + Cl_{other}$$

(See p. 23.)

Equation for Calculating Organ Clearance of a Drug

2-2 $$Cl_{organ} = Q \times \frac{C_{in} - C_{out}}{C_{in}} \text{ or } Cl_{organ} = QE$$

(See p. 24.)

Elimination Rate Constant (*K*) for First-Order, One-Compartment Model

3-1 $$\text{slope} = -K = \frac{\ln C_1 - \ln C_2}{t_1 - t_0}$$

(See p. 34.)

or:

$$-K = \frac{\ln \frac{C_1}{C_2}}{t_1 - t_0}$$

Concentration at Any Given Time, Based on a Previous Concentration (C_0) and K for First-Order, One-Compartment Model

3-2 $$C = C_0 e^{-Kt}$$

(See p. 34.)

where:

C = plasma drug concentration at time = t,
C_0 = plasma drug concentration at time = 0,
K = elimination rate constant,
t = time after dose, and
e^{-Kt} = percent or fraction remaining after time (t).

Note: used often to calculate Cp_{min} from Cp_{max}.

Calculation of $T½$ from K, or K from $T½$ for First-Order, One-Compartment Model

3-3 $$T_{1/2} = \frac{0.693}{K}$$

(See p. 36.)

or:

$$K = \frac{0.693}{T_{1/2}}$$

Mathematical Relationship Between Systemic Clearance (Cl_t) to Both V and K for First-Order, One-Compartment Model

3-4 $$Cl_t / V = K$$

(See p. 37.)

or:

$$Cl_t = V \times K \text{ or } V = Cl_t / K$$

Calculation of Area Under the Plasma Drug Concentration Curve (AUC) and Its Relationship to Both Drug Clearance ($K \times V$) and Dose Administered

3-5 $$AUC = \frac{\text{dose administered}}{\text{drug clearance}}$$

(See p. 38.)

or:

$$\text{drug clearance} = \frac{\text{dose administered}}{AUC}$$

or:

$$AUC = \frac{\text{initial concentration } (C_0)}{\text{elimination rate constant } (K)}$$

Accumulation Factor When Not at Steady State for a One-Compartment, First-Order Model

4-1 $$\text{accumulation factor} = \frac{(1 - e^{-nK\tau})}{(1 - e^{-K\tau})}$$

(See p. 52.)

Accumulation Factor When at Steady State for a One-Compartment, First-Order Model

4-2 $$\frac{1}{(1 - e^{-K\tau})}$$

(See p. 56.)

Calculation of Average Drug Concentration from AUC and Dosing Interval or from Dose/Cl

$$\bar{C} = \frac{AUC}{\tau}$$

and because:

$$AUC = \frac{\text{dose}}{\text{drug clearance}}$$

$$\bar{C} = \frac{\text{dose}}{\text{drug clearance} \times \tau}$$

or:

4-3 $$\bar{C} = \frac{\text{dose}}{Cl_t \times \tau}$$

(See p. 57.)

Cockcroft–Gault Equations for Calculating Creatinine Clearance (CrCl) in Men and Women

9-1 $$CrCl_{male} = \frac{(140 - age)IBW}{72 \times SCr}$$

(See p. 141.)

or:

$$CrCl_{female} = \frac{(0.85)(140 - age)IBW}{72 \times SCr}$$

Note: IBW = ideal body weight.

Equations for Estimating IBW in Men and Women

9-2 IBW_{males} = 50 kg + 2.3 kg for each inch over 5 feet in height

(See p. 141.)

$IBW_{females}$ = 45.5 kg + 2.3 kg for each inch over 5 feet in height

Adjusted Body Weight (AdjBW) Equation for Patients Whose Total Body Weight (TBW) Is More Than 35% Over Their IBW

9-3 $$AdjBW = IBW + 0.4(TBW - IBW)$$

(See p. 141.)

Michaelis–Menten Equation (MME)

10-1 $$\text{daily dose} = \frac{V_{max}C}{K_m + C}$$

(See p. 152.)

or:

$$\text{daily dose}\,(K_m + C) = V_{max}C$$

$$\text{daily dose}\,(K_m) + \text{daily dose}\,(C) = V_{max}C$$

$$\text{daily dose}\,(C) = V_{max}C - \text{daily dose}\,(K_m)$$

Note: relates V_{max}, K_m, plasma drug concentration, and daily dose (at steady state) for zero-order (i.e., nonlinear) model.

Calculation of K_m, the Michaelis Constant (mg/L), Representing the Drug Concentration at Which the Rate of Elimination Is Half the Maximum Rate (V_{max}) for Zero-Order (i.e., Nonlinear) Model

10-2 $$\text{slope} = -K_m = \frac{\text{dose}_{initial} - \text{dose}_{increased}}{\text{dose}/C_{initial} - \text{dose}/C_{increased}}$$

(See p. 152.)

Calculating Steady-State Concentration from Estimates of K_m, V_{max}, and Dose (Rearrangement of the MME) for Zero-Order (i.e., Nonlinear) Model

10-3 $$C = \frac{K_m(\text{daily dose})}{V_{max} - \text{daily dose}}$$

(See p. 153.)

Aminoglycoside Dosing Equations

Calculation of Population Estimates for *K* Based on CrCl

12-1 $$K = 0.00293\,(CrCl) + 0.014$$

(See p. 183.)

Calculation of Population Estimates for Volume of Distribution (*V*) Based on Body Weight or $AdjBW_{AG}$

12-2 $$V = 0.24\ L/kg\ (IBW)$$

(See p. 183.)

or:

$$V = 0.24\ L/kg\ AdjBW_{AG}$$

where:

12-3 $$AdjBW_{AG} = IBW + 0.1(TBW - IBW)$$

(See p. 183.)

Calculation of Best Dosing Interval (τ) Based on Desired Peak and Trough Concentrations

12-4 $$\tau = \frac{1}{-K}(\ln C_{\text{trough (desired)}} - \ln C_{\text{peak (desired)}}) + t$$

(See pp. 186 and 194.)

where t is the duration of the infusion in hours.

Note: should be rounded off to a practical dosing interval such as every 8 hours, every 12 hours, etc.

Calculation of Initial Maintenance Dose (K_0) Based on Estimates of K, V, Desired C_{peak}, and τ

5-1 $$C_{\text{peak (steady state)}} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

(See p. 74.)

where:

$C_{\text{peak(steady state)}}$ = desired peak drug concentration at steady state (milligrams per liter),

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour),

V = volume of distribution (population estimate for aminoglycosides, in liters),

K = elimination rate constant (population estimate for aminoglycosides, in reciprocal hours),

t = duration of infusion (hours), and

τ = desired or most appropriate dosing interval (hours).

Calculation of C_{trough} Concentration Expected from Dose (K_0) and Dosing Interval Used (τ)

3-2 $$C = C_0 e^{-Kt}$$

(See p. 34.)

or:

$$C_{\text{trough(steady state)}} = C_{\text{peak(steady state)}} e^{-Kt'}$$

(See p. 34 and **Equation 3-2**.)

where $t' = \tau$ – time of infusion (t), or the change in time from the first concentration to the second.

Calculation of Loading Dose Based on Initial Calculated Maintenance Dose and Accumulation Factor

12-5 $$\text{loading dose} = \frac{K_0}{(1-e^{-K\tau})}$$

(See p. 189.)

where:

K_0 = estimated maintenance dose,

$1/(1 - e^{-K\tau})$ = accumulation factor at steady state, and

τ = dosing interval at which estimated maintenance dose is given.

Calculation of Patient-Specific (i.e., Actual) K Based on Two Drug Concentrations and Dosing Interval

3-1 $$K = \frac{\ln C_{\text{trough}} - \ln C_{\text{peak}}}{\tau - t}$$

(See p. 34.)

or:

$$-K = \frac{\ln C_{\text{peak}} - \ln C_{\text{trough}}}{\tau - t}$$

Remembering a rule of logarithms: $\ln a - \ln b = \ln (a/b)$, we can simplify this equation for hand-held calculators:

$$K = -\frac{\ln\left(\frac{C_{\text{trough}}}{C_{\text{peak}}}\right)}{\tau - t}$$

or:

$$-K = \frac{\ln\left(\frac{C_{\text{peak}}}{C_{\text{trough}}}\right)}{\tau - t}$$

Either equation may be used to calculate K.

Calculation of Patient-Specific (i.e., Actual) *V* Based on Actual *K*, and Dose (K_0), τ, and Two Drug Concentrations

5-1 $$C_{peak\ (steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

(See p. 74.)

where:

$C_{peak(steady\ state)}$ = C_{peak} measured at steady state,
K_0 = maintenance dose infused at time C_{peak} and C_{trough} were measured,
V = patient's actual volume of distribution that you are trying to determine based on C_{peak} and C_{trough} values,
K = elimination rate constant calculated from patient's C_{peak} and C_{trough} values,
t = duration of infusion (hours), and
τ = patient's dosing interval at time C_{peak} and C_{trough} were measured.

Calculation of Actual (i.e., New) Dosing Interval Based on Patient-Specific Value for *K*

12-4 $$\tau = \frac{1}{-K}(\ln C_{trough\ (desired)} - \ln C_{peak\ (desired)}) + t$$

(See pp. 186 and 194.)

where t is the duration of infusion in hours and K is the actual elimination rate calculated from patient's peak and trough values.

Calculation of Patient-Specific or Adjusted Maintenance Dose (K_0) Based on Actual Values for *K* and *V*

5-1 $$C_{peak\ (steady\ state)} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}$$

(See p. 74.)

where:

$C_{peak(steady\ state)}$ = desired steady-state C_{peak};
K_0 = drug infusion rate (also adjusted maintenance dose you are trying to calculate, in milligrams per hour);
V = actual volume of distribution determined from patient's measured C_{peak} and C_{trough} values, in liters;
K = actual elimination rate constant calculated from patient's measured C_{peak} and C_{trough} values, in reciprocal hours;
t = infusion time, in hours; and
τ = adjusted dosing interval rounded to a practical number.

Calculation of New Expected $C_{trough(steady\ state)}$ That Would Result from New Maintenance Dose and Interval Used

$$C_{trough\ (steady\ state)} = C_{peak\ (steady\ state)}e^{-Kt'}$$

(See p. 34 and **Equation 3-2**.)

where K is actual patient-specific K.

Calculation of Time to Hold Dose When Actual C_{trough} from Laboratory Is Too High

$$C_{trough\ (steady\ state)(desired)} = C_{trough\ (steady\ state)}e^{-Kt'}$$

where t' is the amount of time to hold the dose after the end of the dosing interval.

Next, take the natural log of both sides:

number = number (t') and then simply solve for t', which is now not an exponent.

Average Dose for Gentamicin or Tobramycin When Given as an Extended-Interval (i.e., Once Daily) Dose Based on Actual Body Weight

X_0 = 5.1 mg/kg actual body weight or adjusted body weight if IBW exceeds actual weight by ≥ 35%

Vancomycin Dosing Equations

Calculation of Population Estimate for *K* Based on CrCl

13-2 $K = 0.00083\ \text{hr}^{-1}\ [\text{CrCl (in mL/min)}] + 0.0044$

(See p. 204.)

Calculation of Population Estimate for Volume of Distribution (*V*) Based on TBW

13-1 $V = 0.9\ \text{L/kg TBW}$

(See p. 204.)

Note that, unlike the aminoglycosides, it is recommended that TBW be used to calculate the volume of distribution.

Calculation of Best Dosing Interval (τ) Based on Desired Peak and Trough Concentrations

13-4 $$\tau = \frac{1}{-K}\left[\ln C_{\text{trough (desired)}} - \ln C_{\text{peak (desired)}}\right] + t + t'$$

(See p. 205 and **Equation 12-4**.)

where:

t = duration of infusion (usually 1 or 2 hours for vancomycin) and

t' = time between end of infusion and collection of blood sample (usually 2 hours).

Calculation of Initial Maintenance Dose (K_0) Based on Estimates of *K*, *V*, Desired C_{peak}, τ, and *t*

13-3 $$C_{\text{peak (steady state)}} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See p. 205 and **Equation 5-1**.)

where:

$C_{\text{peak(steady state)}}$ = desired peak concentration (usually 2 hours after end of infusion),

K_0 = drug infusion rate (dose/infusion time),

t = duration of infusion (usually 1 or 2 hours for vancomycin),

K = estimated elimination rate constant,

V = estimated volume of distribution,

t' = time between end of infusion and collection of blood sample (usually 2 hours) (inclusion of t' is different from the calculation for aminoglycosides because sampling time for vancomycin is often at least 4 hours after the beginning of the infusion), and

τ = desired dosing interval, as determined above.

Calculation of C_{trough} Concentration Expected from Dose (K_0) and Dosing Interval Used (τ)

13-5 $$C_{\text{trough}} = C_{\text{peak(steady state)}} e^{-Kt''}$$

(See p. 206 and **Equation 3-2**.)

where t'' is the difference in time between the two plasma concentrations.

Calculation of Patient-Specific (i.e., Actual) *K* Based on Two Drug Concentrations and Dosing Interval

$$K = -\frac{\ln C_{\text{trough}} - \ln C_{\text{peak}}}{\tau - t - t'}$$

(See **Equation 3-1**.)

Calculation of Patient-Specific (i.e., Actual) *V* Based on Actual *K* from Two Drug Concentrations, Dose (K_0), and τ

13-3 $$C_{\text{peak (steady state)}} = \frac{K_0(1 - e^{-Kt})}{VK(1 - e^{-K\tau})} e^{-Kt'}$$

(See p. 205.)

where $C_{\text{peak(steady state)}}$ = measured steady-state peak plasma concentration drawn 2 hours after end of infusion.

Calculation of Actual (i.e., New) Dosing Interval Based on Patient-Specific Value for *K*

13-4 $$\tau = \frac{1}{-K}\left[\ln C_{\text{trough (desired)}} - \ln C_{\text{peak (desired)}}\right] + t + t'$$

(See p. 205.)

Calculation of Patient-Specific Maintenance Dose (K_0) Based on Actual Values for *K* and *V*

13-3 $$C_{\text{peak (steady state)}} = \frac{K_0(1-e^{-Kt})}{VK(1-e^{-K\tau})}e^{-Kt'}$$

(See p. 205.)

where:

$C_{\text{peak(steady state)}}$ = desired peak concentration at steady state,

K_0 = drug infusion rate (also maintenance dose you are trying to calculate, in milligrams per hour),

V = volume of distribution,

K = elimination rate constant calculated from C_{peak} and C_{trough},

t = infusion time (usually 1 or 2 hours),

t' = time from end of infusion until concentration is determined (usually 2 hours for peak), and

τ = desired or most appropriate dosing interval.

Calculation of New Expected $C_{\text{trough(steady state)}}$ That Would Result from New Maintenance Dose and Interval Used

13-5 $$C_{\text{trough(steady state)}} = C_{\text{peak(steady state)}}e^{-Kt''}$$

(See p. 206.)

where t'' is now the number of hours between the peak and trough ($t'' = \tau - t - t'$).

Calculation of Time to Hold Dose When Actual C_{trough} from Laboratory Is Too High

$$C_{\text{trough(desired)}} = C_{\text{trough(actual)}}e^{-Kt}$$

(See p. 34 and **Equation 3-2.**)

where t is the amount of time to hold the dose.

Next, take the natural log of both sides: number = number (t') and then simply solve for t' which is now not an exponent.

Theophylline Dosing Equations

Equation for Calculating the Volume of Distribution for Theophylline and Aminophylline

14-1 $$V(\text{L}) = \text{weight (kg)} \times 0.5\ \text{L/kg}$$

(See p. 223.)

Equation for Calculating a Loading Dose of Theophylline or Aminophylline

14-2 $$\text{D} = \frac{\text{Cpd}V}{SF}$$

(See p. 223.)

Equation for Calculating Clearance for Theophylline or Aminophylline

14-3 $$\text{Cl} = (0.04\ \text{L/kg/hr}) \times \text{weight (kg)}$$

(See p. 223.)

Equation for Calculating a Theophylline or Aminophylline Maintenance Dose

14-4 $$\text{D} = \frac{\overline{C}\,p_{ss}\,\text{Cl}\tau}{SF}$$

(See p. 224.)

Phenytoin Dosing Equations

Calculation of Population Estimate for Volume of Distribution (V)

$$V = 0.65 \text{ L/kg}$$

Michaelis–Menten Constant, Representing the Concentration of Phenytoin at Which the Rate of Enzyme-Saturable Hepatic Metabolism Is One-Half of Maximum ($\frac{1}{2}V_{max}$)

$$K_m = 4 \text{ mg/L}$$

Maximum Amount of Drug That Can Be Metabolized per Unit Time

$$V_{max} = 7 \text{ mg/kg/day}$$

Note: usually expressed as mg/day.

Calculation of Phenytoin Loading Dose

1-1 $$X_0 = \frac{V \times C_{desired}}{S}$$

(See p. 10.)

where:

- V = volume of distribution estimate of 0.65 L/kg,
- $C_{desired}$ = concentration desired 1 hour after the end of the infusion, and
- S = salt factor.

Two Representations of Michaelis–Menten Equation Used to Calculate Daily Dose [X_0/τ (S)] or Expected Serum Concentration C_{ss}

10-1 $$X_0/\tau(S) = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See p. 152.)

15-1 $$C_{ss} = \frac{X_0/\tau(S) \times K_m}{V_{max} - X_0/\tau(S)}$$

(See p. 233.)

Calculation of Time (in Days) for Phenytoin Dosing Regimen to Reach Approximately 90% of Its Steady-State Concentration

10-4 $$t_{90\%} = \frac{K_m \times V}{(V_{max} - X_d)^2}\left[(2.3 \times V_{max}) - (0.9 \times X_d)\right]$$

(See p. 154.)

where:

- X_d = daily dose of phenytoin (in milligrams per day),
- V = volume of distribution,
- V_{max} = maximum rate of drug metabolism (in milligrams per day), and
- K_m = Michaelis–Menten constant.

Phenytoin Dosing Methods

Method 1A (Empiric)

Use 5 mg/kg/day.

Method 1B (Population Parameters)

Use population estimates for the Michaelis–Menten values for K_m of 4 mg/L and V_{max} of 7 mg/kg/day and solve the general MME formula as shown below:

$$X_0/\tau(S) = \frac{V_{max} \times C_{ss\text{–desired}}}{K_m + C_{ss\text{–desired}}}$$

Method 2 (One Steady-State Level)

Use this method after you have one steady-state phenytoin serum drug concentration to solve for V_{max} while still using the population parameter for K_m.

First, to solve for V_{max}:

10-1 $$V_{max} = \frac{(X_d \times S)(K_m + C_{ss\text{-lab}})}{C_{ss\text{-lab}}}$$

(See p. 152.)

where:

V_{max} = calculated estimate of patient's V_{max},
K_m = population estimate of 4 mg/L,
$X_d \times S$ = patient's daily dose of phenytoin free acid, and
C_{ss} = reported steady-state concentration.

Second, after solving for this "better" value for V_{max}, use it plus the old K_m value in the MME to re-solve for dose, as shown below:

10-1 $$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See p. 152.)

where:

$X_d \times S$ = new dose of phenytoin (either free acid or salt),
C_{ss} = desired steady-state concentration (usually 15 mg/L),
K_m = population estimate of 4 mg/L, and
V_{max} = calculated estimate from above.

Method 3 (Two Steady-State Levels)

Use after you have two steady-state phenytoin concentrations from two different phenytoin doses. You can now work another equation to solve for a better value for K_m (shown below). Then use this better K_m value to once again re-solve for an even better V_{max} value than used in Method 2. Once you get new (i.e., real) K_m and V_{max}, re-solve the MME equation for dose.

First, solve for "real" K_m. The slope of the line, which represents $-K_m$, can now be calculated as follows:

10-2 $$-K_m = \frac{X_1 - X_2}{\frac{X_1}{C_1} - \frac{X_2}{C_2}}$$

(See p. 152.)

where:

X = dose (where X is milligrams of free acid) and
C = concentration.

Next, we substitute this new value for K_m into the MME and solve for a V_{max} as follows:

10-1 $$V_{max} = \frac{(X_d \times S)(K_m + C_{ss})}{C_{ss}}$$

(See p. 152.)

where:

$X_d \times S$ = either of the doses the patient received, expressed as free acid,
C_{ss} = steady-state concentration at the dose selected, and
K_m = calculated value.

Finally, we substitute our new V_{max} value (mg/day) and our calculated K_m value (mg/mL) into the MME and solve for X_d as follows:

10-1 $$X_d \times S = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

(See p. 152.)

Digoxin Dosing Equations

Volume of Distribution of Digoxin in Patients with Normal Renal Function

15-2 V_{ss} = 4 to 9 L/kg IBW (average, 6.7 L/kg IBW)

(See p. 242.)

Equation for Estimating Total Systemic Clearance for Digoxin

15-3 $$Cl_t = (1.303 \times CrCl) + Cl_m$$

(See p. 242.)

where:

Cl_t is expressed as mL/minute,

Cl_m = 40 mL/minute in patients with no or mild heart failure, and

= 20 mL/minute in patients with moderate to severe heart failure.

Equation Showing Relationship between Steady-State Plasma Concentration, Maintenance Dose, and Total Systemic Clearance

15-4 $$C_{ss} = \frac{X_d \times 10^6 \times F}{Cl_t \times \tau}$$

(See p. 243.)

APPENDIX B
Supplemental Problems*

QUESTIONS

SP1. Antipyrine (a drug used for pharmacologic and pharmacokinetic studies in the evaluation of hepatic mixed-function oxidase activity) was administered as a single intravenous (IV) bolus dose (1200 mg). The following plasma drug concentration and time data were collected:

Time after Dose (hours)	Plasma Drug Concentration (mg/L)
2	26.1
4	24.3
8	20.7
18	14.2
32	8.6
48	4.5

Using semilog graph paper, determine the approximate time after the dose when the plasma drug concentration falls to 3.0 mg/L.

A. 50 hours
B. 40 hours
C. 70 hours
D. 60 hours

SP2. Using the same data for antipyrine dosing above, estimate the volume of distribution.

A. 50.2 L
B. 42.9 L
C. 45.3 L
D. 24.9 L

*These problems supplement material presented in Lessons 1–11.

SP3. Just after an IV dose of antibiotic X, the plasma drug concentration was 7.3 mg/L. Six hours later, the concentration was 2.9 mg/L. Predict the plasma drug concentration at 10 hours after the dose.

A. 2.9 mg/L
B. 2.1 mg/L
C. 1.63 mg/L
D. 3.1 mg/L

SP4. The following plasma drug concentration and time data were obtained after an IV bolus dose of procainamide (420 mg):

Time after Dose (hours)	Plasma Drug Concentration (mg/L)
0	3.86
0.5	3.36
1.0	3.00
2.0	2.29
3.0	1.77
5.0	1.06
7.0	0.63
10.0	0.29

Calculate clearance by the area method.

A. 27.83 L/hour
B. 19.4 L/hour
C. 33.6 L/hour
D. 11.8 L/hour

SP5. What will be the minimum concentration after the thirteenth IV dose of drug X if C_{max} equals 100 mg/L after the first dose, K equals 0.4 hr^{-1}, and τ equals 6 hours? (Assume an IV bolus dose model.)

A. 8.98 mg/L
B. 9.98 mg/L
C. 13.9 mg/L
D. 7.36 mg/L

SP6. An IV bolus dose of antibiotic Q (500 mg) was administered to a patient on an every-6-hour schedule. Predict the plasma drug concentrations at 3 and 6 hours after dosing. Assume: (1) a one-compartment model, (2) $T½$ = 4.95 hours, (3) Cl_t = 14.2 L/hour, and (4) the attainment of steady state.

A. 5.7 and 3.7 mg/L, respectively
B. 7.1 and 9.8 mg/L, respectively
C. 3.7 and 2.9 mg/L, respectively
D. 6.9 and 5.7 mg/L, respectively

SP7. For the same patient, predict the plasma concentrations at 3 and 6 hours after the second dose.

A. 6.46 and 5.02 mg/L, respectively
B. 3.32 and 2.19 mg/L, respectively
C. 8.12 and 5.78 mg/L, respectively
D. 4.64 and 3.05 mg/L, respectively

SP8. An 80-kg patient receives 500 mg of drug Y intravenously by bolus injection every 6 hours. Assume that V = 0.5 L/kg, and $T½$= 6.4 hours. Predict the steady-state peak and trough concentrations.

A. 28.6 and 14.7 mg/L, respectively
B. 26.2 and 13.7 mg/L, respectively
C. 24.3 and 12.9 mg/L, respectively
D. 19.8 and 9.6 mg/L, respectively

SP9. Calculate the theophylline clearance (Cl_t) for a 52-kg patient receiving a continuous IV infusion of aminophylline at 75 mg/hour. The patient's steady-state plasma theophylline concentration with this dose rate is 20.2 mg/L. Assume that the patient's V = 0.45 L/kg. Remember, aminophylline = 80% theophylline.

A. 2.97 L/hour
B. 3.75 L/hour
C. 3.71 L/hour
D. 2.37 L/hour

SP10. The following plasma concentration and time data were collected after a single 500-mg IV dose of amikacin:

Time after Dose (hours)	Amikacin Concentration (mg/L)
2	22.5
4	18.4
8	12.3
16	5.6
24	2.5
36	0.75
48	0.23

Calculate K, V_{area}, and Cl_t for this patient.

A. 0.20 hr^{-1}, 28.2 L, and 2.82 L/hour, respectively

B. 0.01 hr^{-1}, 1.82 L, and 0.182 L/hour, respectively

C. 0.10 hr^{-1}, 18.2 L, and 1.82 L/hour, respectively

D. 0.10 hr^{-1}, 182 L, and 18.2 L/hour, respectively

SP11. Seven healthy female subjects were each given 1250 mg of an experimental drug (BB-K8) by IV bolus administration. The drug follows first-order kinetics. The following mean plasma concentration and time data were obtained:

Time after Dose (hours)	Mean Plasma Drug Concentration (mg/L)
0	116.0
0.08	108.3
0.17	92.8
0.25	83.3
0.50	59.2
0.75	38.2
1.0	30.6
1.5	22.9
2.0	19.7
3.0	13.2
4.0	9.3
5.0	7.3
6.0	5.1
7.0	4.1
8.0	2.8

Plot the plasma concentration versus time profile on semilog paper. From your graph, determine A, B, α, β, V_{area}, and Cl_t (in milliliters per minute).

A. 3.60 hr^{-1}, 0.41 hr^{-1}, 39.1 L, and 11 L/hr, respectively

B. 2.60 hr^{-1}, 0.31 hr^{-1}, 29.1 L, and 9 L/hr, respectively

C. 1.60 hr^{-1}, 0.21 hr^{-1}, 19.1 L, and 7 L/hr, respectively

D. 4.60 hr^{-1}, 0.35 hr^{-1}, 49.1 L, and 12 L/hr, respectively

SP12. Calculate V_{area} given the data in Supplemental Problem 1. Compare it with the V calculated (using the back-extrapolation method) in Supplemental Problem 2.

A. 54.6 L

B. 43.6 L

C. 10.3 L

D. 42.96 L

SP13. An outpatient had been taking 400 mg of phenytoin per day for 1 month and had a plasma concentration of 6.0 mg/L when sampled 6 hours after the dose. Because of continued seizures, the dose was increased to 500 mg/day. Four weeks later, the patient was seen in a clinic, and the plasma drug concentration 6 hours after the dose was 9.0 mg/L (assume steady state). The physicians asked that the dose be increased to provide a plasma concentration of 12 mg/L 6 hours after the dose. What dose would you recommend?

A. 552 mg phenytoin free acid/day

B. 600 mg phenytoin free acid/day

C. 652 mg phenytoin free acid/day

D. 900 mg phenytoin free acid/day

ANSWERS

SP1. A, B, C. *Incorrect answers*

D. CORRECT ANSWER

SP2. A, C, D. *Incorrect answers*

B. CORRECT ANSWER

$$C_0 = 28 \text{ mg/L}$$

$$V = \frac{\text{dose}}{C_0} = \frac{1200 \text{ mg}}{28 \text{ mg/L}} = 42.9 \text{ L}$$

SP3. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. First, calculate the elimination rate constant (K):

$$K = -\frac{(\ln 7.3 - \ln 2.9)}{(0 - 6 \text{ hr})} = 0.15 \text{ hr}^{-1}$$

Then use these equations:

$$C = C_0 e^{-Kt}$$

$$C_{\text{at } 10 \text{ hr}} = (7.3 \text{ mg/L}) e^{-0.15 \text{ hr}^{-1}(10 \text{ hr})}$$

$$= 1.63 \text{ mg/L}$$

SP4. A. CORRECT ANSWER. To calculate clearance by the area method, we need to know the area under the plasma concentration curve (AUC) and the dose (X_0). Therefore, it is first necessary to calculate AUC using the trapezoidal method as shown below. Note that one way to indicate an AUC from one time point to another is as $AUC_{0 \rightarrow 0.5}$, which means AUC from 0 to 0.5 hour.

$$AUC_{0 \rightarrow 0.5} = \frac{(3.84 \text{ mg/L} + 3.36 \text{ mg/L})}{2} \times (0.5 - 0 \text{ hr})$$
$$= 1.80 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{0.5 \rightarrow 1} = \frac{(3.36 + 3.00)}{2} \times (1 - 0.5) = 1.59 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{1 \rightarrow 2} = \frac{(3.00 + 2.29)}{2} \times (2 - 1) = 2.65 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{2 \rightarrow 3} = \frac{(2.29 + 1.77)}{2} \times (3 - 2) = 2.03 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{2 \rightarrow 3} = \frac{(2.29 + 1.77)}{2} \times (3 - 2) = 2.03 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{3 \rightarrow 5} = \frac{(1.77 + 1.06)}{2} \times (5 - 3) = 2.83 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{5 \rightarrow 7} = \frac{(1.06 + 0.63)}{2} \times (7 - 5) = 1.69 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{7 \rightarrow 10} = \frac{(0.63 + 0.29)}{2} \times (10 - 7) = 1.38 \text{ (mg/L)} \times \text{hr}$$

$$AUC_{10 \rightarrow \infty} = \frac{C_{10 \text{ hr}}}{K} = \frac{0.29 \text{ mg/L}}{0.26 \text{ hr}^{-1}} = 1.12 \text{ (mg/L)} \times \text{hr}$$

$$AUC = 1.80 + 1.59 + 2.65 + 2.03 + 2.83 + 1.69 + 1.38 + 1.12$$
$$= 15.09 \text{ (mg/L)} \times \text{hr}$$

$$Cl_t = \frac{X_0}{AUC} = \frac{420 \text{ mg}}{15.09 \text{ (mg/L)} \times \text{hr}} = 27.83 \text{ L/hr}$$

B, C, D. *Incorrect answers*

SP5. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. To determine C_{min} after the thirteenth dose, first calculate C_{max} after the thirteenth dose using the multiple-dose equation:

$$C_{max(nth\ dose)} = C_{max(nth\ dose)} \frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}$$

$$C_{max13} = C_{max1} \frac{(1-e^{-13K\tau})}{(1-e^{-K\tau})}$$

$$= (100\ mg/L) \frac{(1-e^{(-13)(0.4\ hr^{-1})(6\ hr)})}{(1-e^{(-0.4\ hr^{-1})(6\ hr)})}$$

$$= 110\ mg/L$$

Then:

$$C_{min13} = C_{max13} e^{-K\tau} = (110\ mg/L) e^{(-0.4\ hr^{-1})(6\ hr)}$$

$$= 9.98\ mg/L$$

SP6. A. CORRECT ANSWER. To predict plasma concentrations 3 and 6 hours after a dose at steady state, we should first estimate the C_{max} (at 0 hour after the dose) using the steady-state IV equation:

$$C_{max} = \frac{X_0}{V(1-e^{-K\tau})}$$

So we first need to estimate V and K. V can be estimated from:

$$Cl_t = VK$$

Then:

$$V = \frac{Cl_t}{K} = \frac{14.2\ L/hr}{\left(\frac{0.693}{4.95\ hr}\right)}$$

$$V = 101.43\ L$$

Note that:

$$K = \frac{0.693}{T\frac{1}{2}} = 0.14\ hr^{-1}$$

Then:

$$C_{max} = \frac{500\ mg}{(101.43\ L)(1-e^{-0.14\ hr^{-1}(6\ hr)})}$$

$$= 8.67\ mg/L$$

From C_{max}, the concentration at any time after a dose can be calculated by:

$$C_t = C_{max} e^{-Kt}$$

So:

$$C_{3\ hr} = (8.67\ mg/L)(e^{-0.14\ hr^{-1}(6\ hr)})$$

$$= 5.7\ mg/L$$

and:

$$C_{6\ hr} = (8.67\ mg/L)(e^{-0.14\ hr^{-1}(6\ hr)})$$

$$= 3.74\ mg/L$$

B, C, D. *Incorrect answers*

SP7. A, B, C. *Incorrect answers*

D. CORRECT ANSWER. The equations used to solve Supplemental Problem 5 can be used here, with the number of doses (n) equal to 2 rather than 13:

$$C_{max(2nd\ dose)} = \frac{X_0(1-e^{-nK\tau})}{V(1-e^{-K\tau})}$$

$$= \frac{(500\ mg)(1-e^{(-2)(-0.14\ hr^{-1})(6\ hr)})}{(101.43\ L)(1-e^{(-0.14\ hr^{-1})(6\ hr)})}$$

$$= 7.06\ mg/L$$

Then:

$$C_t = C_{max} e^{-Kt}$$

$$C_{3\ hr} = (7.06\ mg/L)(e^{(-0.14\ hr^{-1})(6\ hr)})$$

$$= 4.64\ mg/L$$

and:

$$C_{6\ hr} = (7.06\ mg/L)(e^{(-0.14\ hr^{-1})(6\ hr)})$$

$$= 3.05\ mg/L$$

SP8. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. First, determine K and total V:

$$V = 0.5\ L/kg \times 80\ kg = 40\ L$$

$$K = \frac{0.693}{T\,1/2} = \frac{0.693}{6.4\ hr} = 0.108\ hr^{-1}$$

Then use the steady-state multiple-dose equation (for IV bolus doses):

$$C_{peak} = \frac{X_0}{V}\left(\frac{1}{1-e^{-K\tau}}\right)$$

$$= \frac{500\ mg}{(40\ L)(1-e^{-0.108\ hr^{-1}(6\ hr)})}$$

$$= 26.2\ mg/L$$

$$C_{trough} = C_{peak}e^{-K\tau}$$

$$= (26.2\ mg/L)e^{-0.108\ hr^{-1}(6\ hr)}$$

$$= 13.7\ mg/L$$

SP9. A. CORRECT ANSWER. To calculate clearance, use the relationship:

$$Cl_t = \frac{K_0}{C_{ss}} = \frac{75\ mg/hr\ (0.80)}{20.2\ mg/L} = 2.97\ L/hr$$

B, C, D. *Incorrect answers*

SP10. A, B, D. *Incorrect answers*

C. CORRECT ANSWER. First, the data should be plotted on semilog graph paper to determine if they are linear or nonlinear. When the points are determined to make a straight line, any two may be chosen to calculate K. (It is best, however, to choose two that are not close to each other, such as 2 and 4 hours.) So:

$$K = -\frac{\Delta Y}{\Delta X} = -\left(\frac{\ln 0.75 - \ln 22.5}{36\ hr - 2\ hr}\right) = 0.10\ hr^{-1}$$

Then:

$$T\,1/2 = \frac{0.693}{K} = 6.93\ hr$$

To calculate V_{area} and Cl_t, we should first estimate the AUC. With a one-compartment, first-order model after IV administration, the calculation of AUC is simplified. In this case:

$$AUC = \frac{C_0}{K}$$

where C_0 is determined by $C_t = C_0e^{-Kt}$. For $t = 2$ hours:

$$22.5\ mg/L = C_0e^{-0.10\ hr^{-1}(2\ hr)}$$

Then:

$$C_0 = 27.5\ mg/L$$

and:

$$AUC = \frac{27.5\ mg/L}{0.1\ hr^{-1}}$$

$$= 275\ mg/L \times hr$$

Then:

$$V_{area} = \frac{X_0}{AUC \times K}$$

$$= \frac{500 \text{ mg}}{(275 \text{ mg/L} \times \text{hr})(0.10 \text{ hr}^{-1})}$$

$$= 18.2 \text{ L}$$

$$Cl_t = \frac{X_0}{AUC}$$

$$= \frac{500 \text{ mg}}{(275 \text{ mg/L} \times \text{hr})} = 1.82 \text{ L/hr}$$

Note that the use of AUC for calculation of clearance generally produces a more accurate estimate than the use of $Cl_t = K \times V$.

SP11. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. A, B, α, and β will be calculated using residuals. First, back-extrapolate the terminal (straight-line) portion of the plot and estimate the back-extrapolated points. Determine the residual points by subtracting the back-extrapolated concentrations from the actual concentrations.

Actual Points		Back Extrapolated Points		Residual Points
108.3	–	32.0	=	76.3 mg/L
92.8	–	31.0	=	61.8 mg/L
83.3	–	30.0	=	53.3 mg/L
59.2	–	28.0	=	31.2 mg/L
38.2	–	26.0	=	12.2 mg/L
30.6	–	24.0	=	6.6 mg/L
22.9	–	21.0	=	1.9 mg/L

Then plot the residual points on the same graph. From the back-extrapolated line, the intercept = B (equals 33 mg/L) and the terminal slope gives β:

$$\beta = \frac{\ln 2.8 - \ln 13.2}{8 \text{ hr} - 3 \text{ hr}} = -0.31$$

$$= 0.31 \text{ hr}^{-1}$$

Then from the residual line, the intercept = A (equals 84 mg/L) and the slope gives α:

$$\alpha = \frac{\ln 1.9 - \ln 76.3}{1.5 \text{ hr} - 0.08 \text{ hr}} = -2.60$$

$$= 2.60 \text{ hr}^{-1}$$

To calculate V_{area} and Cl_t, the AUC must first be determined. The AUC can be estimated using the trapezoidal rule or by adding the area of each exponential equation:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} = 32.3 + 106.5$$

$$= 138.8 \text{ (mg/L)} \times \text{hr}$$

Then:

$$V_{area} = \frac{\text{dose}}{AUC \times \beta}$$

$$= \frac{1250 \text{ mg}}{[138.8 \text{ (mg/L)} \times \text{hr}](0.31 \text{ hr}^{-1})} = 29.1 \text{ L}$$

$$Cl_t = \frac{\text{dose}}{AUC}$$

$$= \frac{1250 \text{ mg}}{138.8 \text{ mg/L}} = 9.0 \text{ L/hr}$$

SP12. A, B, C. *Incorrect answers*

D. CORRECT ANSWER.

$$V_{area} = \frac{\text{dose}}{AUC \times K}$$

$$K = 0.037 \text{ hr}^{-1}$$

To calculate the AUC, the C_0 must first be estimated from the plot (C_0 = 28 mg/L):

$$AUC_{0\to2} = \frac{(28 + 26.1)(2-0)}{2} = 54.1\ (mg/L)\times hr$$

$$AUC_{2\to4} = \frac{(26.1 + 24.3)(4-2)}{2} = 50.4\ (mg/L)\times hr$$

$$AUC_{4\to8} = \frac{(24.3 + 20.7)(8-4)}{2} = 90.0\ (mg/L)\times hr$$

$$AUC_{8\to18} = \frac{(20.7 + 14.2)(18-8)}{2} = 174.5\ (mg/L)\times hr$$

$$AUC_{18\to32} = \frac{(14.2 + 8.6)(32-18)}{2} = 159.6\ (mg/L)\times hr$$

$$AUC_{32\to48} = \frac{(8.6 + 4.5)(48-32)}{2} = 104.8\ (mg/L)\times hr$$

$$AUC_{48\to\infty} = \frac{C_{48}}{K} = \frac{4.5\ mg/L}{0.037\ hr^{-1}} = 121.6\ (mg/L)\times hr$$

Then:

$$AUC = 54.1 + 50.4 + 90.0 + 174.5 + 159.6 + 104.8 + 121.6$$

$$= 755\ (mg/L)\times hr$$

$$V_{area} = \frac{X_0}{AUC\times K}$$

$$= \frac{1200\ mg}{[755\ (mg/L)\times hr](0.037\ hr^{-1})}$$

$$= 42.96\ L$$

So, in this case, the two estimates for V are similar.

SP13. A, C, D. *Incorrect answers*

B. CORRECT ANSWER. Phenytoin follows Michaelis–Menten (saturable) pharmacokinetics. To determine V_m and K_m, the daily dose must be plotted (y-axis) versus the daily dose divided by the resulting steady-state concentrations (x-axis). From a plot of the dose (y-axis) versus dose/concentration (x-axis), the following are observed:

V_m = 1000 mg daily (which is equal to the y-intercept)

K_m = 9.0 mg/L (which equals –slope)

Then:

$$dose = \frac{V_m C_{ss}}{K_m + C_{ss}}$$

where:

C_{ss} = 12 mg/L, the desired concentration:

$$= \frac{(1000\ mg)(12\ mg/L)}{9.0\ mg/L + 12\ mg/L} = 571\ mg/day$$

Therefore, the likely daily dose would be 600 mg/day.

Alternatively, you can use **Equation 10-2**, p. X, to calculate $-K_m$ from these two doses and two levels. Both methods should give the same answer.

APPENDIX C
Glossary

Area under the first moment curve (AUMC)—the area under the first moment curve (drug concentration × time) versus time (moment) curve, an important model-independent pharmacokinetic parameter.

Area under the plasma concentration versus time curve (AUC)—the area formed under the curve when plasma drug concentration is plotted versus time. Drug clearance is equal to the dose administered divided by AUC.

Bioavailability (*F*)—the fraction of a given drug dose that reaches the systemic circulation.

Biopharmaceutics—the study of the relationship between the nature and intensity of a drug's biologic effects and various drug formulation or administration factors, such as the drug's chemical nature, inert formulation substances, pharmaceutical processes used to manufacture the dosage form, and routes of administration.

Clearance—the process of removing a drug from plasma (expressed as volume of plasma per a given unit of time).

Clinical pharmacokinetics—the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Compartmental model—a basic type of model used in pharmacokinetics. Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one-compartment, two-compartment, and multi-compartment models. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids.

Drug distribution—transport processes that deliver drug to body tissues and fluids after absorption.

50% effective concentration (EC_{50})—the concentration at which 50% of the maximum drug effect is achieved.

Elimination rate constant (*K*)—a constant representing the fraction of drug removed per unit of time (in units of reciprocal time, usually hr^{-1}).

Extraction ratio (E)—the fraction of drug removed from plasma by one pass through an organ. This ratio is a number between 1 and 0. Organs that are very efficient at eliminating a drug will have an extraction ratio approaching 1 (i.e., 100% extraction).

First-order elimination—when the amount of drug eliminated from the body in a specific time is dependent on the amount of drug in the body at that time. A straight line is obtained from the natural log of plasma drug concentration versus time plot only for drugs that follow first-order elimination.

First-pass effect—drug metabolism by the liver that occurs after absorption but before the drug reaches the systemic circulation.

Formation clearance ($CL_{P \to mX}$)—a model-independent parameter that provides a meaningful estimate of a drug's fractional metabolic clearance.

Half-life ($T½$)—the amount of time necessary for a plasma drug concentration to decrease by half.

Kinetic homogeneity—the predictable relationship between plasma drug concentration and concentration at the receptor site.

Mean residence time (MRT)—the average time for intact drug molecules to transit or reside in the body.

Minimum inhibitory concentration—the lowest concentration of an antibacterial agent that will inhibit the visible growth of a microorganism after overnight incubation.

Model—a simplified mathematical simulation of physiologic processes used to predict the time course of drug concentrations or effect in the body.

Model-independent parameter—a pharmacokinetic parameter, such as clearance, that can be calculated without the use of a specific model.

Model-independent pharmacokinetics—pharmacokinetic calculations using parameters that do not require the use of specific compartmental models (e.g., one-compartment, two-compartment, etc.).

Pharmacodynamics—the relationship between drug concentrations at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects.

Pharmacokinetics—the relationship of drug dose to the time course of drug absorption, distribution, metabolism, and excretion.

Plasma—the fluid portion of blood (including soluble proteins but not formed elements).

Receptor—a structure on the surface of a cell to which a drug binds and causes an effect within the cell.

Serum—the fluid portion of blood that remains when the soluble protein fibrinogen is removed from plasma.

Steady state—the point at which, after multiple doses, the amount of drug administered over a dosing interval equals the amount of drug being eliminated over that same period.

Therapeutic drug monitoring—determination of plasma drug concentrations and clinical data to optimize a patient's drug therapy.

Therapeutic range—the plasma concentration range that is effective and safe in treating specific diseases.

Tolerance—decreased drug effectiveness with continued use.

Volume of distribution (V)—an important indicator of the extent of drug distribution into body fluids and tissues, V relates the amount of drug in the body to the measured concentration in the plasma. Thus, V is the volume required to account for all of the drug in the body if the concentration in all tissues is the same as the plasma concentration.

Volume of distribution at steady state (V_{ss})—a parameter that relates total amount of drug in the body to a particular plasma concentration under steady-state conditions.

Zero-order elimination—when the amount of drug eliminated for each time interval is constant, regardless of the amount of drug in the body.

INDEX

Page numbers followed by *f* refer to figures; those followed by *t* refer to tables.

A

B

C

D

E

F

N

O

Q

R

S

T

Z

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